Supreme Court, U.S.
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No.

IN THE
Supreme Court of the United States

AVENTIS PHARMA S.A.
AND AVENTIS PHARMACEUTICALS INC.,
Petitioners,

v.

AMPHASTAR PHARMACEUTICALS, INC.
AND TEVA PHARMACEUTICALS USA, INC.,
Respondents.

On Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Under the judge-made doctrine of "inequitable conduct," a federal court may decline to enforce an otherwise valid patent that was procured through fraud or deceit. *Precision Instrument Mfg. Co.* v. *Auto. Maint. Mach. Co.*, 324 U.S. 806 (1945). As befits the punitive nature of the doctrine, this Court has invoked it only in extreme circumstances involving "deliberate," "corrupt," "sordid" and "highly reprehensible" misconduct. Some panels of the Federal Circuit have similarly limited the inequitable conduct doctrine to deliberately planned and carefully executed schemes to defraud, but other Federal Circuit panels—including the majority in this case—have adopted a "sliding scale" under which "less intent" is required as the materiality of an omission or misrepresentation increases. The question presented is:

Whether a court may refuse to enforce an otherwise valid patent on the basis of an inequitable conduct determination premised on a sliding scale between intent and materiality, effectively permitting a finding of fraudulent intent to be predicated on gross negligence.

PARTIES TO THE PROCEEDING AND RULE 29.6 STATEMENT

Pursuant to this Court's Rule 29.6, counsel for petitioners certifies that:

Petitioner Aventis Pharma S.A. has no direct parent companies. All corporations that own 10 percent or more of petitioner Aventis Pharma S.A. are: Aventis Inc., Sanofi-Aventis Europe, Sanofi-Aventis, and sanofi-aventis Amerique du Nord.

Petitioner Aventis Pharmaceuticals Inc. is a subsidiary of Aventis Holdings Inc., which is a subsidiary of Aventis Inc., which is a subsidiary of sanofi-aventis Amerique du Nord. A minority interest in Aventis Pharmaceuticals Inc. is held by Aventis Beteiligungsverwaltung GmbH, which is a wholly-owned subsidiary of Hoechst GmbH, which is a wholly-owned subsidiary of Sanofi-Aventis Europe, which is a wholly-owned subsidiary of Sanofi-Aventis.

TABLE OF CONTENTS

Page

OPINIONS BELOW 1

JURISDICTION 1

STATUTORY PROVISION INVOLVED 1

STATEMENT 2

REASONS FOR GRANTING THE PETITION 10

I. THE DECISION BELOW DISREGARDS THIS COURT'S PRECEDENT AND CONFLICTS WITH TRADITIONAL PRINCIPLES OF EQUITY 10

II. THE LOWER COURT DECISIONS ARE IN CONFLICT 19

III. THE ISSUE WARRANTS THIS COURT'S ATTENTION 24

CONCLUSION 31

TABLE OF APPENDICES

Page

APPENDIX A: Opinion of the United States Court of Appeals for the Federal Circuit 1a

APPENDIX B: Opinion of the United States District Court for the Central District of California 39a

APPENDIX C: Order of the United States Court of Appeals for the Federal Circuit Denying Panel Rehearing and Rehearing En Banc 92a

APPENDIX D: Prior opinion of the United States Court of Appeals for the Federal Circuit 95a

APPENDIX E: Prior opinion of the United States District Court for the Central District of California 110a

TABLE OF AUTHORITIES

Page(s)

CASES

Am. Hoist & Derrick Co. v. *Sowa & Sons, Inc.*, 725 F.2d 1350 (Fed. Cir. 1984) 12, 21, 22, 29

Anza v. *Ideal Steel Supply Corp.*, 126 S. Ct. 1991 (2006).....26

Brasseler, U.S.A. I, L.P. v. *Stryker Sales Corp.*, 267 F.3d 1370 (Fed. Cir. 2001) 7, 13

Buckman Co. v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001) 27

Burlington Indus. v. *Dayco Corp.*, 849 F.2d 1418 (Fed. Cir. 1988) 22

Carter-Wallace, Inc. v. *Davis Edwards Pharmacal Corp.*, 443 F.2d 867 (2d Cir. 1971).....20

Critikon, Inc. v. *Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253 (Fed. Cir. 1997) 7

DeLong Corp. v. *Raymond Int'l, Inc.*, 622 F.2d 1135 (3d Cir. 1980) 20

Digital Equip. Corp. v. *Diamond*, 653 F.2d 701 (1st Cir. 1981) 20, 21

Dollar Sys., Inc. v. *Avcar Leasing Sys., Inc.*, 890 F.2d 165 (9th Cir. 1989).....21

TABLE OF AUTHORITIES - Continued

Page(s)

eBay Inc. v. *MercExchange LLC*,
547 U.S. 388 (2006) 15, 17, 18

Eresch v. *Braecklein*,
133 F.2d 12 (10th Cir. 1943) 21

Ernst & Ernst v. *Hochfelder*,
425 U.S. 185 (1976) 13, 15, 16

Exxon Shipping Co. v. *Baker*,
128 S. Ct. 2605 (2008) 30

Ferring B.V. v. *Barr Labs., Inc.*,
437 F.3d 1181 (Fed. Cir. 2006) 6, 23

Fid. Fed. Bank & Trust v. *Kehoe*,
126 S. Ct. 1612 (2006) 25

FMC Corp. v. *Manitowoc Co., Inc.*,
835 F.2d 1411 (Fed. Cir. 1987) 13, 14, 22

GFI, Inc. v. *Franklin, Corp.*,
265 F.3d 1268 (Fed. Cir. 2001) 22

Graham v. *John Deere Co.*,
383 U.S. 1 (1966) 18

Haloro, Inc. v. *Owens-Corning Fibreglas Corp.*, 266 F.2d 91[illegible] (D.C. Cir. 1959) 20

Hazel-Atlas Glass Co. v. *Hartford-Empire Co.*, 322 U.S. 238 (1944) ..... *passim*

TABLE OF AUTHORITIES - Continued

Page(s)

Hecht Co. v. *Bowles*, 321 U.S. 321 (1944).....17

Hoffmann-La Roche, Inc. v. *Promega Corp.*, 323 F.3d 1354 (Fed. Cir. 2003).....25

Holmes Group, Inc. v. *Vornado Air Circulation Sys., Inc.*, 535 U.S. 826 (2002).....21

J.P. Stevens Co. v. *Lex Tex, Ltd.*, 747 F.2d 1553 (Fed. Cir. 1984).....22

Keystone Driller Co. v. *General Excavator Co.*, 290 U.S. 240 (1933).....*passim*

Kingsdown Med. Consultants, Ltd. v. *Hollister, Inc.*, 863 F.2d 867 (Fed. Cir. 1988).....22, 23, 24

Kohler v. *Kohler & Co.*, 319 F.2d 634 (7th Cir. 1963).....16

Koon v. *United States*, 518 U.S. 81 (1996).....29

KSR International Co. v. *Teleflex Inc.*, 127 S. Ct. 1727 (2007).....18

Lord v. *Goddard*, 54 U.S. 198 (1851).....14

Madigan v. *Telemarketing Assocs.*, 538 U.S. 600 (2003).....14, 16

TABLE OF AUTHORITIES - Continued

Page(s)

Magee v. *Manhattan Life Ins. Co.*,
92 U.S. 93 (1875) 14

McKesson Info. Solutions, Inc. v.
Bridge Med., Inc.,
487 F.3d 897 (Fed. Cir. 2007) 27

MedImmune, Inc. v. *Genentech, Inc.*,
549 U.S. 118 (2007) 15

Microsoft Corp. v. *AT&T Corp.*,
550 U.S. 437 (2007) 15

Moss v. *Riddle & Co.*,
9 U.S. 351 (1809) 14

Myzel v. *Fields*,
386 F.2d 718 (8th Cir. 1967) 16

Paragon Podiatry Lab., Inc. v. *KLM Labs., Inc.*,
984 F.2d 1182 (Fed. Cir. 1993) 5

Parker v. *Motorola*,
524 F.2d 518 (5th Cir. 1975) 20

Pfizer, Inc. v. *Int'l Rectifier Corp.*,
538 F.2d 180 (8th Cir. 1976) 20

Philadelphia Newspapers, Inc. v. *Hepps*,
475 U.S. 767 (1986) 19

Praxair, Inc. v. *ATMI, Inc.*,
543 F.3d 1306 (Fed. Cir. 2008) 23, 24

TABLE OF AUTHORITIES - Continued

Page(s)

Precision Instrument Mfg. Co. v. *Auto. Maint. Mach. Co.*, 324 U.S. 806 (1945) .....*passim*

Reilly v. *Pinkus*, 338 U.S. 269 (1949) 14

Scott Paper Co. v. *Fort Howard Paper Co.*, 432 F.2d 1198 (7th Cir. 1970).....20

Star Scientific, Inc. v. *R.J. Reynolds Tobacco Co.*, 537 F.3d 1357 (Fed. Cir. 2008) 23, 24

Stoneridge Inv. Partners, LLC v. *Scientific-Atlanta, Inc.*, 128 S. Ct. 761 (2008).....26, 30

True Temper Corp. v. *CF&I Steel Corp.*, 601 F.2d 495 (10th Cir. 1979).....20

United States v. *Am. Bell Tel. Co.*, 167 U.S. 224 (1897).....13

Weinberger v. *Romero-Barcelo*, 456 U.S. 305 (1982).....18

Wiscart v. *D'Auchy*, 3 U.S. 321 (1796).....14

CONSTITUTIONAL PROVISION

U.S. Const., art. I, § 8, cl. 8 2

TABLE OF AUTHORITIES - Continued

Page(s)

STATUTES AND REGULATION

28 U.S.C. § 1254(1) 1

35 U.S.C. § 271(e)(2) 3

35 U.S.C. § 282 1

37 C.F.R. § 1.56 (2006) 16

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TABLE OF AUTHORITIES - Continued

Page(s)

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PETITION FOR A WRIT OF CERTIORARI

Aventis Pharma S.A. and Aventis Pharmaceuticals Inc. respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The opinion of the court of appeals (App., *infra*, 1a-38a) is reported at 525 F.3d 1334. The opinion of the district court (App., *infra*, 39a-91a) is reported at 475 F. Supp. 2d 970. A previous opinion of the court of appeals (App., *infra*, 95a-109a) is electronically reported at 176 Fed. Appx. 117, and that of the district court (App., *infra*, 110a-143a) at 390 F. Supp. 2d 936.

JURISDICTION

The judgment of the court of appeals was entered on May 14, 2008. Aventis's timely petition for rehearing was denied on September 25, 2008. App., *infra*, 92a-94a. On November 10, 2008, the Chief Justice extended the time to file this petition until January 23, 2009. 08A417. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

Section 282 of the Patent Act, 35 U.S.C. § 282, provides, in relevant part:

> The following shall be defenses in any action involving the validity or infringement of a patent and shall be pleaded:
>
> (1) Noninfringement, absence of liability for infringement or unenforceability . . . .

STATEMENT

After undertaking a comprehensive review of the American patent system, the National Academies of Science and Engineering concluded that the costs and uncertainties associated with the "inequitable conduct" doctrine counsel its elimination or reform. National Research Council, A Patent System for the 21st Century (2004) at 123, http://www.nap.edu/html/patentsystem/0309089107.pdf. In reaching this conclusion, the Academies singled out for criticism the very standard at issue in this case: the inference of "intent from the materiality of the information that was withheld." *Ibid.* This is the standard on which the district court found Aventis guilty of "inequitable conduct," and, as a result, held Aventis's patent (for a drug with over $2 billion in annual U.S. sales) entirely unenforceable. Applying the same standard, the Federal Circuit, in a 2-1 decision, affirmed.

This case presents the Court with an ideal opportunity to clarify the circumstances in which a patent holder may be stripped by a district court of extremely valuable patent rights—a frequently recurring question with profound ramifications for the patent system's ability to foster and encourage innovation, as required under the constitutional mandate "to promote the Progress of . . . useful Arts." U.S. Const., art. I, § 8, cl. 8.

1. Aventis invented novel compositions of low molecular weight heparins used in the prevention and treatment of thromboses (*i.e.*, blood clotting), and the process for making these compositions. Aventis applied for a patent, which issued in 1995 after a lengthy review process in which the Patent and Trademark Office carefully scrutinized the nov-

elty and other features of Aventis's claims. *See* U.S. Patent No. 5,389,618 ("the '618 patent"). Aventis began marketing and selling the compositions in the United States after the United States Food and Drug Administration approved them for sale in 1993 under the name Lovenox®. Lovenox® currently brings in some $3.1 billion in annual revenue, with U.S. sales exceeding $2 billion annually.

2. In 2003, Aventis sued respondents Amphastar Pharmaceuticals, Inc. and Teva Pharmaceuticals USA, Inc. under 35 U.S.C. § 271(e)(2) for infringing the '618 patent by submitting an application to the FDA for approval to manufacture and sell generic versions of Lovenox® before the expiration of the patent. Respondents counterclaimed, accusing Aventis of having procured the patent through "inequitable conduct."

Respondents premised their inequitable conduct theory on a simple omission made by Dr. André Uzan, a non-inventor expert whose help on limited matters involving biology was sought because the inventor, Roger Debrie, was a chemist. Dr. Uzan is a distinguished scientist who has been inducted into the French Legion of Honor for his scientific contributions and lifetime dedication to the public health, a recipient of France's highest award for drug discovery (the Galien Research Prize), and an expert with the French Ministry of Public Health and the French Court of Appeals. C.A. App. 1917-28.

Dr. Uzan's involvement with the prosecution of the patent was confined to three isolated instances: providing the information in Example 6 of the '618 patent, a declaration submitted to the PTO nearly three years thereafter, and a second declaration submitted one year after the first. Example 6 was

meant to "illustrate[] the increase in stability" of the invention compared to prior art, App., *infra*, 43a-44a n.3, measured by the increase in plasma half-life (longer half-life means greater stability). In making this comparison in Example 6 (and in his later declarations), Dr. Uzan disclosed the 40 mg and 60 mg dosages of the invention, but failed to disclose that the prior art composition was at 60 mg, and thus that he was making a comparison at different doses.[1]

Although it is undisputed that Dr. Uzan knew the dose of the prior composition, there was no evidence indicating that Dr. Uzan intentionally failed to disclose that information. The full prior art study that Dr. Uzan utilized for his comparison does disclose the dose, but the photocopied, unaltered half-

---

[1] The omission was made in Subsection 3 of Example 6, which provides as follows:

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.
>
> A first pharmacokinetic study was carried out on volunteers between 21 and 30 years of age. . . . . The results obtained were as follows:
>
> (1) From the mixtures [of the present invention]:
>
> *40 mg dose:* in 75% of the cases, the half-life was longer than 4 hours, and was even longer than 4½ hours in approximately 45% of the cases;
>
> *60 mg dose:* in 75% of the cases, the half-life was longer than 3.7 hours.
>
> (2) . . .
>
> (3) When the product was prepared according to the process described in [the prior art], the half-life was longer than 4½ hours in 17% of the cases.
>
> (4) . . .

App., *infra*, 43a-44a n.3.

life data table (Table III) that he consulted when providing information to the Aventis patent department does not. C.A. App. 1148; 1226.

3. In early 2003, Aventis filed a reissue application for the '618 patent. The PTO reissued the patent on June 14, 2005, with all of the original independent claims, but without Example 6. U.S. Patent No. RE 38,743.

The reissue was granted a day before the district court granted Amphastar's summary judgment motion that the '618 patent was unenforceable. App., *infra*, 38a. In an appeal of this decision, the Federal Circuit affirmed the district court's finding of high materiality, but rejected the finding of deceptive intent as inappropriate on summary judgment. *Id.* at 106a. Under Federal Circuit precedent, Aventis—the party charged with inequitable conduct—was required to demonstrate its innocence in order to prevent a finding of deceptive intent on summary judgment, *i.e.*, it "was required to state specific facts supporting a plausible justification or excuse for its failure to disclose material information." *Ibid.* (citing *Paragon Podiatry Lab., Inc.* v. *KLM Labs., Inc.*, 984 F.2d 1182, 1191 (Fed. Cir. 1993)).

Finding that "Aventis has met its burden of setting forth a plausible justification for its failure to disclose material information," the Federal Circuit reversed and remanded for a trial on inequitable conduct. App., *infra*, 106a. Aventis had explained, among other things, that Dr. Uzan could not have intended to deceive the PTO, because a comparison at different doses was common industry practice and reasonable for clinical reasons. Because the 60 mg dosage for the invented composition caused bleeding in some patients, the 40 mg dosage was therapeuti-

cally preferable for some indications, and thus was the relevant dosage to compare against the 60 mg dosage of the prior art. The district court had rejected this explanation as irrelevant, but the Federal Circuit disagreed, noting that "[t]he reasonableness of the comparison between different dosages is relevant to determining whether the failure to disclose . . . was made with an intent to deceive." *Ibid.*

4. On remand, after a bench trial, the district court found inequitable conduct, holding that respondents had presented evidence that "'there has been a failure to supply highly material information and . . . the record establishes that (1) the applicant knew of the information; (2) the applicant knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding.'" App., *infra*, 87a (quoting *Ferring B.V.* v. *Barr Labs., Inc.*, 437 F.3d 1181, 1191 (Fed. Cir. 2006)).

"Regarding knowledge," the district court held that "there is no debate that Dr. Uzan knew the dose[] used in the [prior study] and at trial, Dr. Uzan admitted to knowing that he was comparing the half-lives . . . at different doses." App., *infra*, 87a-88a. This was undisputed. It also was, however, of limited significance, as it only showed that Dr. Uzan knew that the dosage of the prior composition was 60 mg, not that he realized that he omitted that dosage information.

"Regarding knowledge of materiality," the district court held, "it was obvious that a reasonable [patent examiner] would have considered dosage important." App., *infra*, 87a-88a. This test, however, is the test for materiality, not for intent.

The district court acknowledged that it was effectively eliminating the requirement that a patent applicant have actual knowledge that the omitted information is material and may mislead the PTO, but viewed this as supported by Federal Circuit precedent. "Contrary to Aventis' arguments," the district court explained, "it is well-established that proof of actual knowledge is not always necessarily required" to prove intent to deceive. App., *infra*, 82a n.18. Knowledge that the omitted information is material and may deceive the PTO can simply be presumed instead from materiality: individuals who fail to supply highly material information "should have known" about the information's materiality. *Ibid.* (quoting *Brasseler, U.S.A. I, L.P.* v. *Stryker Sales Corp.*, 267 F.3d 1370, 1376 (Fed. Cir. 2001)); *see also ibid.* ("a patentee's failure to appreciate the legal significance of the facts that it failed to disclose d[oes] not absolve it" of a finding of deliberate deception) (citing *Critikon, Inc.* v. *Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1256-57 (Fed. Cir. 1997)).

The district court also rejected as "incredible" evidence of Dr. Uzan's subjective belief that the comparison at different but therapeutic doses was reasonable. App., *infra*, 87a.

Based on its two findings of non-disclosure and high materiality, and *Aventis's* failure to prove that it was innocent, the district found "intent to deceive." App., *infra*, 87a (finding inequitable conduct because "[t]he elements of nondisclosure and high materiality have been admitted, and no credible excuse demonstrated").

5. On appeal, a divided panel of the Federal Circuit affirmed, with the majority applying the same sliding-scale standard as the district court. App., *in-*

fra, 18a ("'The more material the omission or misrepresentation, the less intent that must be shown to elicit a finding of inequitable conduct'") (citation omitted). Under this standard, the Federal Circuit majority, like the district court, presumed fraudulent intent from materiality, and shifted the burden to Aventis to clearly and convincingly prove the absence of such intent.

For example, critical to respondents' charge of inequitable conduct was their claim that the comparison discussed in Example 6 and in Dr. Uzan's declarations was meant to show not only the superior stability of the invention, but also a compositional difference between the invention and prior art—in which case a comparison at different doses would have been improper. Example 6 nowhere mentions or discusses compositional difference, and by its very own terms states that it is meant to address the superior "stability" of the invention, *i.e.*, a property of the invention. App., *infra*, 5a ("This example illustrates the increase in stability, in vivo, of the mixtures of the invention"). Instead of requiring respondents to clearly and convincingly prove that Example 6 *was meant* to address a compositional difference, the panel majority turned the burden of proof on its head, requiring instead that Aventis clearly and convincingly show that Example 6 *was not meant* to address compositional difference: "Nothing in example 6 suggests that the half-life comparison was designed to show only [superior stability] and not [a compositional difference]." *Id.* at 23a.

In dissent, Judge Rader criticized the improper "[m]erging [of] intent and materiality" under the majority's sliding-scale standard, and highlighted several previous cases in which the Federal Circuit had "emphasized materiality almost to the exclusion of

[the] intent requirement." App., *infra*, 33a. According to Judge Rader, Dr. Uzan's omission, even if material and negligent, could not reasonably support an inference of "culpable intent to deceive," a finding which is reserved only to "the most extreme cases of fraud and deception." *Id.* at 31a.

Key to Judge Rader's analysis was the absence of any evidence that Dr. Uzan knowingly omitted the information. *See* App., *infra*, 35a ("To make it clear, Dr. Uzan did not attempt to conceal data that were otherwise present. Rather he just submitted the study without adding to the disclosure."). Furthermore, the absence of a dosage in subsection 3 of Example 6, given its presence in subsections 2 and 4, was "blatantly obvious." *Id.* at 36a. "[I]f Dr. Uzan had intended to deceive the USPTO, he would not have made this omission so conspicuous." *Ibid.* In addition, Judge Rader found it simply hard to believe, absent clear evidence to the contrary, that a "world-class scientist would . . . risk his reputation and tarnish his brilliant career for . . . a patent for an invention in which he was not even involved." *Ibid.*

Judge Rader also pointed out that, aware of the allegations of inequitable conduct brought by respondents, the PTO nonetheless reissued the patent, including all original independent claims, without Example 6 and without reliance on the challenged comparisons of the half-life/stability data. According to Judge Rader, this rendered both materiality and intent "suspect." App., *infra*, 38a.

Aventis petitioned for en banc review, arguing (among other things) that the sliding-scale standard "effectively dispens[es] with the separate element of 'intent' in inequitable conduct cases involving a ma-

terial omission." Pet. C.A. Reh'g Br. 1. The Federal Circuit declined the invitation to clean its own house.

REASONS FOR GRANTING THE PETITION

The courts below invoked the "inequitable conduct" doctrine to render unenforceable an extremely valuable patent twice granted by the responsible agency of the executive branch (under authority conferred by Congress pursuant to a constitutional mandate), thereby depriving Aventis of the exclusive rights to its invention. And the lower courts did so without requiring the type of outright perjury and other extreme misconduct to which this Court has reserved the doctrine. That was wrong.

As Judge Rader recognized in his dissent, decisions like this one impair the effective functioning of the patent system. A lax standard for inequitable conduct not only encourages unwarranted litigation and threatens investments in research and development, but also interferes with the ability of the PTO to effectively examine patent applications by encouraging applicants to deluge the PTO with hundreds of minimally relevant references.

Numerous judges, scholars, practitioners and national organizations have recommended abolition or reform of the inequitable conduct doctrine. This Court has not revisited the doctrine in more than 60 years, the lower court decisions are in conflict, and the internally divided Federal Circuit has been unable to rein in the unwarranted expansion of the doctrine. It is time.

I. THE DECISION BELOW DISREGARDS THIS COURT'S PRECEDENT AND CONFLICTS WITH TRADITIONAL PRINCIPLES OF EQUITY

A. In three—and only three—cases, this Court has refused to enforce a patent for inequitable conduct in its prosecution or enforcement. Each in-

volved extreme circumstances of "deliberate," "corrupt," "sordid," and "highly reprehensible" fraudulent conduct intentionally committed by the patent holder during prosecution or enforcement of the patent.

Keystone Driller Co. v. *General Excavator Co.*, 290 U.S. 240 (1933), for example, involved a "corrupt transaction" that was "highly reprehensible," in which the patent owner obtained, in exchange for "valuable considerations," both a false affidavit and false deposition testimony "to keep secret the details of [a] prior use" which would have been "sufficient to cast doubt upon the validity of the patent." *Id.* at 243-44.

Hazel-Atlas Glass Co. v. *Hartford-Empire Co.*, 322 U.S. 238 (1944), involved the grant of "[e]quitable relief against [a] fraudulent judgment[]." *Id.* at 248. There, the patentee paid generously for the fabrication of an "ostensibly disinterested" publication describing the claimed invention as a "remarkable advance in the art," which was submitted to the PTO and relied on by the patentee in the Court of Appeals. *Id.* at 240, 248. The purported author was also paid to submit a false affidavit. This "sordid story," *id.* at 243, "a deliberately planned and carefully executed scheme to defraud not only the Patent Office but the Circuit Court of Appeals," *id.* at 245, came out only after judgment had been entered. Based upon "settled equitable principles," the Court ordered the judgment set aside. *Id.* at 247.

And *Precision Instrument Manufacturing Co.* v. *Automotive Maintenance Machinery Co.*, 324 U.S. 806 (1945), involved a situation in which "the history of the patents" was "steeped in perjury and undisclosed knowledge of perjury," *id.* at 816, including false testimony by Larson (the patentee) in an interference proceeding, and the discovery of Larson's per-

jury by Automotive, which used that information to blackmail Larson into assigning his patent rights to Automotive and agreeing never to contest the resulting patent. The result of these actions was that Automotive, which never revealed the patent's fraudulent ancestry to the Patent Office, was issued a patent with claims broader than those to which Automotive was actually entitled. Explaining that "he who comes into equity must come with clean hands" (*i.e.*, to have acted "without fraud or deceit"), the Court declined to enforce the patent. *Id.* at 814-15.[2]

Notwithstanding this Court's careful confining of inequitable conduct to "deliberately planned and carefully executed scheme[s] to defraud," *Hazel-Atlas*, 322 U.S. at 245, the Federal Circuit has permitted, in this case and others, a lesser showing of intent in cases in which the materiality of the alleged improper conduct is high. App., *infra*, 18a ("The more material [a patent applicant's] omission or misrepresentation, the less intent that must be shown"). Under this sliding scale of intent and materiality, high materiality "necessarily" disposes of the need to prove a deliberate deception as required under this Court's precedent: a high showing of materiality "would necessarily create an inference that its nondisclosure was 'wrongful.'" *Am. Hoist & Derrick Co.* v. *Sowa & Sons, Inc.*, 725 F.2d 1350, 1363 (Fed. Cir.

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[2] Unlike *Keystone* and *Hazel-Atlas*, *Precision Instrument* (like this case), involved conduct that occurred solely before the PTO, and not in the action before the court. The standard applied in *Keystone* and *Hazel-Atlas*, on which *Precision Instrument* itself relied, was nevertheless applicable: To the extent that courts may punish allegedly fraudulent conduct that occurred solely before a co-equal branch of the government, the standard should be no less than that applicable to an alleged fraud on the court.

1984). A knowing deception is thus presumed from the mere fact that highly material information was omitted, under the justification that "he who failed to supply highly material information *should have known* about the information's materiality." App., *infra*, 81a (quoting *Brasseler, U.S.A. I, L.P.* v. *Stryker Sales Corp.*, 267 F.3d 1370, 1376 (Fed. Cir. 2001)) (emphasis added). But, as early as 1897, this Court recognized that one challenging a patent as fraudulently or wrongfully obtained must prove fraud by "clear and convincing" evidence, and the courts may not "assume[] the existence of a knowledge which no one had; of an intention which is not shown." *United States* v. *Am. Bell Tel. Co.*, 167 U.S. 224, 259 (1897). The Federal Circuit engages in precisely such an assumption under its "should have known" standard.

The non-disclosure of material information is a necessary but not sufficient element of fraud or inequitable conduct. The complainant must also prove that the material information was *intentionally* withheld. The Federal Circuit, by presuming intent from materiality, effectively does away with the separate requirement for intent, permitting a finding of intent to be predicated on strict liability for a material omission. That the patent holder is then allowed to prove his innocence (a "credible" explanation for the non-disclosure) does not cure the infirmity of this standard. Indeed, where, as here, a defending party is given the ability to show a "reasonable" explanation for a non-disclosure which would otherwise trigger strict liability, this Court has deemed the standard to be one of "negligence." *Ernst & Ernst* v. *Hochfelder*, 425 U.S. 185, 208 (1976). And the Federal Circuit itself has couched the "should have known" standard in terms of gross negligence. *See FMC Corp.* v. *Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987) ("an applicant who knew of the art or information cannot intentionally avoid

learning of its materiality through gross negligence, *i.e.*, it may be found that the applicant 'should have known' of that materiality"); *see also id.* at n.9 ("'gross negligence' was seen as occurring when a reasonable person 'should have known of the materiality of a withheld reference'") (citation omitted).

But neither negligence nor strict liability can sensibly be reconciled with the deliberately fraudulent conduct required by this Court's patent decisions. Those decisions limit the inequitable conduct doctrine to deliberate schemes to defraud involving extreme circumstances of outright perjury (*Precision Instrument*), or intentionally false and fabricated evidence and testimony (*Hazel-Atlas* and *Keystone*)—not mere negligent failures to disclose.

B. Nor can the Federal Circuit's sliding scale be reconciled with the Court's decisions involving fraud or inequitable conduct allegations in other areas of the law. For more than two centuries, the Court has repeatedly reiterated that "[f]raud means an intention to deceive." *Lord* v. *Goddard*, 54 U.S. 198, 211 (1851); *see also Wiscart* v. *D'Auchy*, 3 U.S. 321, 330 (1796) ("fraud must always principally depend upon the *quo animo*," *i.e.*, on the animus or bad faith); *Moss* v. *Riddle & Co.*, 9 U.S. 351, 357 (1809) (stating that "[f]raud consists in the intention"); *Magee* v. *Manhattan Life Ins. Co.*, 92 U.S. 93, 98-99 (1875) ("To constitute fraud, the intent to deceive must clearly appear. The concealment must be wilful and intentional.") (citation omitted); *Reilly* v. *Pinkus*, 338 U.S. 269, 275 (1949) (findings of fraud are justified by representations "made with intent to deceive"); *Madigan* v. *Telemarketing Assocs.*, 538 U.S. 600, 621 (2003) ("the gravamen of the fraud action . . . is particular representations made with intent to mislead").

In no fraud case has this Court ever indicated that intent to deceive could be judged on a sliding scale, with gross negligence sufficient in cases of high materiality. To the contrary, *Ernst & Ernst* explicitly precludes a gross negligence approach. 425 U.S. at 191 n.7, 197, 201, 215 (holding that securities fraud requires proof of "intent to deceive," and that this excludes a gross negligence theory of liability).

The relevance of these non-patent cases is beyond serious dispute. The common theme of this Court's recent patent decisions is that patent cases are subject to the same general principles as other claims brought under federal common law or statutory regimes. *See Microsoft Corp.* v. *AT&T Corp.*, 550 U.S. 437 (2007); *MedImmune, Inc.* v. *Genentech, Inc.*, 549 U.S. 118 (2007), *eBay Inc.* v. *MercExchange LLC*, 547 U.S. 388 (2006). If this case had been brought as a fraud case under other federal law regimes, it would not have survived even a motion to dismiss. Even accepting the factual predicates relied on by the courts below (namely, that Dr. Uzan knew the dosage information, that the dosage information was highly material, that Dr. Uzan "should have known" of its materiality, and that Dr. Uzan could not "credibly" prove his innocence (App., *infra*, 87a)), there is still no legally sufficient basis under this Court's precedent to find intent to deceive.

Under that precedent, the test for deception is not whether the defendant "should have known" that an omission was material and misleading, as the courts below inquired. App., *infra*, 82a. Nor is it whether the allegedly defrauded party would have considered the omitted information important (*id.* at 87a-88a), which is the test for materiality. Nor is it whether the accused declarant has proved his innocence. *Ibid.* It is whether *the complainant* has shown that the material and misleading nature of an

omission was known to the declarant himself and that the omission was made with a misleading purpose. As the Court explained in *Madigan*, "[f]alse statement alone does not [result in] fraud liability." 538 U.S. at 621. Rather, "the complainant must show that the defendant made a false representation . . . *knowing that the representation was false*" and, further, "with the intent to mislead the listener." *Ibid.* (emphasis added).

This Court's requirement that the misleading nature of an omission be known to the defendant is flatly at odds with the holding below that "proof of actual knowledge is not always necessarily required" to prove inequitable conduct. App., *infra*, 81a-82a. Two of the cases criticized in *Ernst & Ernst* on the ground that they set too low a standard for fraud, 425 U.S. at 193 n.12, had explicitly held, as in this case, that "knowledge of the falseness of the impression produced by the statements or omissions made[] is not required" to show fraud. *See Myzel* v. *Fields*, 386 F.2d 718, 734-35 (8th Cir. 1967); *Kohler* v. *Kohler & Co.*, 319 F.2d 634, 637-38 (7th Cir. 1963). The PTO has similarly recognized that a standard requiring actual knowledge is the appropriate one for patent law. *See* 37 C.F.R. § 1.56 (2006) (imposing on a declarant the "duty to disclose to the [PTO] all information *known to that individual to be material* to patentability as defined in this section") (emphasis added).[3]

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[3] To be sure, as respondents have claimed, the intentionality of certain conduct can be inferred from circumstantial evidence. For example, if the version of Table III in the study consulted by Dr. Uzan had included the dosage information, but Dr. Uzan had removed it from the version provided to the PTO, this deletion would tend to suggest a knowing omission (albeit not necessarily a purposive one). But no such facts tending to prove an intentional removal of information are present here: the photo-

C. The Federal Circuit's rigid imposition of the drastic remedy of unenforceability—regardless of the absence of extraordinary circumstances, the presence of alternative remedies, and the impact on the public interest—also contravenes well-settled equitable principles, and this Court's decisions interpreting them.

Equitable principles require inquiry into the inadequacy of legal remedies before equitable relief is awarded. *eBay*, 547 U.S. at 391. In defiance of this well-known threshold for equitable relief, the patent was held unenforceable in this case before the court decided whether respondents would have been entitled to relief on their legal defenses of non-infringement and invalidity. App., *infra*, 32a.

Moreover, the Federal Circuit's one-size-fits-all remedy of "unenforceability" as a punishment for inequitable conduct involving broad ranges of culpability does not comport with the equitable nature of the doctrine. "The essence of equity jurisdiction has been the power of the Chancellor to do equity and to mould each decree to the necessities of the particular case. Flexibility rather than rigidity has distinguished it." *Hecht Co.* v. *Bowles*, 321 U.S. 321, 329 (1944). In equity remedies are tailored to fit the circumstances of the particular case, with the harshest remedies chosen in the extraordinary circumstances in which they are the "only means" to safeguard the

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[Footnote continued from previous page]

copied, unaltered half-life data table (Table III) that Dr. Uzan consulted and provided to the PTO did not contain the dosage information. As Judge Rader explained in his dissent, "Dr. Uzan did not attempt to conceal data that were otherwise present. Rather he just submitted the study without adding to the disclosure." App., *infra*, 35a.

public interest sought to be protected, and less invasive means selected otherwise. *Weinberger* v. *Romero-Barcelo*, 456 U.S. 305, 312-15 (1982); *see also eBay*, 547 U.S. at 392 (the harshest remedies do not "automatically" follow a determination that a violation has been committed). For example, in *Romero-Barcelo*, the Court held that the goal of ensuring compliance with the permitting requirement imposed by the statute could be achieved by remedies other than an injunction, such as penalties or fines. 456 U.S. at 312-15.

Similarly here, absent the extraordinary circumstance of deliberate fraud resulting in the issuance of an otherwise invalid patent, unenforceability is not the "the only means of" remedying a non-disclosure and "ensuring compliance" with disclosure obligations, as courts could impose "fines" and other "penalties," *Romero-Barcelo*, 456 U.S. at 314, including a weakened presumption of validity, *see KSR International Co.* v. *Teleflex Inc.*, 127 S. Ct. 1727, 1745 (2007). The Federal Circuit, however, automatically imposes the extraordinary remedy of unenforceability even absent the extraordinary circumstances to which this Court has reserved it in *Precision Instrument*, *Keystone*, and *Hazel-Atlas*.

Nor does the Federal Circuit follow the traditional principle that "[i]n exercising their sound discretion, courts of equity should pay particular regard for the public consequences" of the remedy they impose. *Romero-Barcelo*, 456 U.S. at 312. In fact, as in this case, the Federal Circuit and the lower courts impose the extraordinary remedy of unenforceability without *any* analysis of the impact on the public interest, including the constitutional purpose of promoting innovation. *See Graham* v. *John Deere Co.*, 383 U.S. 1, 6 (1966) ("'promot[ing] the Progress of . . .

useful Arts' . . . is the standard expressed in the Constitution and it may not be ignored").

When life-saving innovations and billions of dollars in annual revenue and research and development are at stake (as here), the need to calibrate the interest in ensuring non-misleading disclosures to the PTO with the constitutional interest in promoting innovation is heightened—both in setting the standard for inequitable conduct and in remedying it. In other balancing situations involving similar burden-shifting, this Court has tipped the scales in favor of the constitutional interest. *See, e.g.*, *Philadelphia Newspapers, Inc.* v. *Hepps*, 475 U.S. 767, 778 (1986) (although placing the burden on the complainant to prove the falsity of defamatory speech "will insulate from liability some speech that is false," "the Constitution requires us to tip [the scales] in favor of protecting true speech" because otherwise there "would be some cases in which defendants could not bear [the burden to prove their innocence] despite the fact that the speech is in fact true"). And in *Precision Instrument*, *Keystone*, and *Hazel-Atlas*, this Court has similarly tipped the balance in favor of the constitutional interest by reserving inequitable conduct to exceptional circumstances. In contrast, the Federal Circuit has not only failed to tip the scales in favor of the constitutional interest—it has failed even to consider that interest.

II. The Lower Court Decisions Are In Conflict

Although this Court has emphasized that fraud and inequitable conduct require a deliberate deception, the lower appellate courts have split regarding the requisite level of culpability, and that division of authority is reflected in the Federal Circuit's own caselaw.

A. Before the creation of the Federal Circuit in 1982, at least five regional circuits rejected a gross negligence predicate for fraud or inequitable conduct. *See Scott Paper Co.* v. *Fort Howard Paper Co.*, 432 F.2d 1198, 1204 (7th Cir. 1970) (finding that the equitable defense of "[u]nclean hands can be asserted only if there has been a deliberate misrepresentation in the [PTO]"); *Carter-Wallace, Inc.* v. *Davis Edwards Pharmacal Corp.*, 443 F.2d 867, 882 (2d Cir. 1971) ("in order for nondisclosure to constitute inequitable misconduct there must be something more than negligence"); *Parker* v. *Motorola*, 524 F.2d 518, 535 (5th Cir. 1975) ("mere negligent omissions or misstatements to the Patent Office do not provide sufficient basis for a finding of fraud"); *Pfizer, Inc.* v. *Int'l Rectifier Corp.*, 538 F.2d 180, 186 (8th Cir. 1976) (same); *see also Haloro, Inc.* v. *Owens-Corning Fibreglas Corp.*, 266 F.2d 918, 919 (D.C. Cir. 1959) (reversing finding of inequitable conduct because the challenged misrepresentations did not involve the type of deliberate fraud and exceptional circumstances at issue in *Precision Instruments* and *Hazel-Atlas*).

Three other circuits premised inequitable conduct on gross negligence, at least in cases of high materiality. *DeLong Corp.* v. *Raymond Int'l, Inc.*, 622 F.2d 1135, 1146 (3d Cir. 1980) (inequitable conduct requires "at least a gross negligence or recklessness in misrepresenting the truth"); *True Temper Corp.* v. *CF&I Steel Corp.*, 601 F.2d 495, 502 (10th Cir. 1979) (rejecting "intentional fraud" as the "only ground for withholding enforcement of patents," and allowing unenforceability "where misrepresentations are made in an atmosphere of gross negligence as to their truth") (internal quotation and citation omitted); *Digital Equip. Corp.* v. *Diamond*, 653 F.2d 701, 716 (1st Cir. 1981). Of the three, the First Circuit is the inventor of the sliding scale. It held, just like

American Hoist (the Federal Circuit case adopting the sliding scale in 1984), that "a lesser showing of [materiality] may suffice when an intentional scheme to defraud is established, whereas a greater showing of the [materiality] would necessarily create an inference that its nondisclosure was 'wrongful.'" *Digital Equip.*, 653 F.2d at 716.

Given the Federal Circuit's inability to resolve this conflict, the split between the regional circuits addressing the inequitable conduct issue presents a compelling case for this Court's review. Not only do regional circuit decisions identify *potent* cases that "merit this Court's attention," *see Holmes Group, Inc.* v. *Vornado Air Circulation Sys., Inc.*, 535 U.S. 826, 839 (2002) (Stevens, J., concurring), but as inequitable conduct is an issue of federal common law, the conflict between the circuits has repercussions beyond the confines of patent law. *Cf. Dollar Sys., Inc.* v. *Avcar Leasing Sys., Inc.*, 890 F.2d 165, 173 (9th Cir. 1989) (holding, outside the patent context, that "grossly negligent" conduct "did not rise to the level of misconduct necessary for the application of the unclean hands doctrine" because "[b]ad intent is the essence of the defense of unclean hands"); *Eresch* v. *Braecklein*, 133 F.2d 12, 14 (10th Cir. 1943) (it is "well-settled" "that it is only fraud or willful misconduct which bars one from recovering in a court of equity under the [inequitable conduct] maxim, 'He who comes into equity must come with clean hands'").

B. The split among the regional circuits is mirrored in the Federal Circuit's own decisions, which are deeply divided between those requiring actual proof of intent to deceive, and those merely presuming it under the sliding-scale standard.

Soon after its creation in 1982, the Federal Circuit adopted the First Circuit's sliding scale of intent and materiality, under which a high showing of ma-

teriality "would necessarily create an inference that its nondisclosure was 'wrongful.'" *Am. Hoist*, 725 F.2d at 1363. Around the same time, the Federal Circuit also adopted a "gross negligence" standard for finding intent to deceive. *J.P. Stevens Co.* v. *Lex Tex, Ltd.*, 747 F.2d 1553 (Fed. Cir. 1984).

Within a few years, inequitable conduct had become a "plague" on patent holders and the court system. *Burlington Indus.* v. *Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988). In response, the en banc Federal Circuit tried to clarify that inequitable conduct was not a remedy for every mistake, blunder, or fault in the patent procurement process. *Kingsdown Med. Consultants, Ltd.* v. *Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc).

Although *Kingsdown* purported to overrule the "gross negligence" standard, it did not discard the sliding scale adopted in 1984 by its *American Hoist* decision. As a result, while paying lip-service to prior decisions that reject gross negligence and reciting the principle that "materiality does not presume intent," courts (as in this case) nonetheless proceed to apply a radically different standard—the sliding scale, with its "necessary[]" inference of intent from high materiality. And, unable to recognize that this "should have known" standard is logically incompatible with its rejection of gross negligence, the Federal Circuit has created a morass of conflicting, confusing, and contradictory decisions. *Compare FMC Corp.* v. *Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987) (equating the "should have known" standard with gross negligence), *with GFI, Inc.* v. *Franklin, Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001) ("[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct") (internal quotation and citation omitted). Thus, some panels understand that intent

and materiality are separate elements, which must *both* be proven *before* any balancing or burden-shifting is undertaken; others (like the majority in this case) deem high materiality sufficient to establish a prima facie case of intent.

In light of this decisional rift, the sliding scale's conflation of materiality and intent is (unsurprisingly) deemed improper by some on the Federal Circuit bench. For example, Judge Newman has noted that the "should have known" standard "replac[es] the need for evidence of intent" with "a positive inference of wrongdoing," and results in decisions in which the court "infers material misrepresentation, infers malevolent intent, presumes inequitable conduct, and wipes out a valuable property right . . . on the theory that the inventor 'should have known' that something might be deemed material." *Ferring*, 437 F.3d at 1196 (Newman, J., dissenting). Judge Rader similarly criticized the improper "[m]erging [of] intent and materiality" caused by the sliding scale, considering that the Federal Circuit has often "emphasized materiality almost to the exclusion of [the] intent requirement." App., *infra*, 33a. Judge Lourie has expressed similar views. *Praxair, Inc.* v. *ATMI, Inc.*, 543 F.3d 1306, 1329 (Fed. Cir. 2008) (Lourie, J., dissenting).

Despite its internal critics and numerous calls for reform, the Federal Circuit has consistently refused to overrule the sliding scale (and its "should have known" test for highly material omissions) en banc. Cases such as *Star Scientific, Inc.* v. *R.J. Reynolds Tobacco Co.*, 537 F.3d 1357 (Fed. Cir. 2008), in which the Federal Circuit scrupulously followed *Kingsdown* and reiterated that materiality and intent are separate elements that must *both* be proven as part of a complainant's prima facie case, before

any burden-shifting is undertaken, cannot overrule the sliding scale unless they are taken en banc. They were not. *See* 2008 U.S. App. LEXIS 25385 (Fed. Cir. Oct. 22, 2008) (denying en banc review in *Star Scientific*). Indeed, no more than a month after the *Star Scientific* decision, the Federal Circuit in *Praxair* again deemed high materiality sufficient to establish intent. 543 F.3d at 1329 (Lourie, J., dissenting) (arguing that the standard applied by the majority and the district court improperly "conflat[ed] intent with materiality").

This case, therefore, does not represent a mere isolated deviation from *Kingsdown*'s disapproval of a gross negligence standard for inequitable conduct. It follows an equally applicable and long-standing precedent, and highlights the entrenched and deepening rift in the Federal Circuit that leaves rights to inventions worth billions of dollars entirely at the mercy of the Federal Circuit's panel selection process. If left uncorrected, this rift will continue to sow substantial confusion in an area of law where settled and clear standards are paramount and (ironically) the *raison d'être* for the Federal Circuit.

III. THE ISSUE WARRANTS THIS COURT'S ATTENTION

A. Inequitable conduct is asserted in virtually every patent infringement case. At the appellate level alone, the Federal Circuit has decided no fewer than 42 inequitable conduct cases over the past three years. Inequitable conduct (or unclean hands) charges are also common outside the patent context, further underscoring the need for this Court's guidance regarding the circumstances and level of culpability that justify application of the doctrine.

This recurring question is of far-reaching national importance. The reflexive resort to charges of inequitable conduct without regard to actual culpability is a "plague" on litigants and the courts. *Hoffmann-La Roche, Inc.* v. *Promega Corp.*, 323 F.3d 1354, 1381 (Fed. Cir. 2003) (Newman, J., dissenting) (commenting on the "New Plague"); *see also* National Association of Manufacturers, Response to the Advisory Commission on Patent Law Reform 10 (1991) (viewing "inequitable conduct" allegations—which "are made with a distressing frequency, litigated at enormous cost, and contribute enormously to the uncertainty of inventors seeking to enforce their rights"—as a "plague").

Although many inequitable conduct charges may not ultimately succeed, *see* Katherine Nolan-Stevaux, *Inequitable Conduct Claims in the 21st Century: Combating the Plague*, 20 Berkeley Tech. L. J. 147, 148-49 (2005), the Federal Circuit's diluted standard for "intent" is far from harmless. A large part of the harm is inflicted by costly discovery, or trials, on unwarranted charges of inequitable conduct that could have been abated on a dispositive motion had this Court's *scienter* requirement been followed. The harm is even greater when inequitable conduct claims prevail even though premised on mere proof of materiality and inferences of intent from materiality, in contravention of this Court's teachings. The "enormous" harm in this case—involving patent rights in a drug with *billions* of dollars in annual sales—is itself "a strong factor in deciding whether to grant certiorari." *Fid. Fed. Bank & Trust* v. *Kehoe*, 126 S. Ct. 1612 (2006) (Scalia, J., concurring in the denial of certiorari).

The uncertainty and expense imposed by the expansive application of the "inequitable conduct" doc-

trine are further magnified by the Federal Circuit's elimination of another meaningful check on unwarranted claims of fraud: the reliance (*i.e.*, causation) requirement normally applicable to claims of fraud and to equitable claims akin to fraud, such as promissory estoppel. *Stoneridge Inv. Partners, LLC* v. *Scientific-Atlanta, Inc.*, 128 S. Ct. 761, 769 (2008); *Anza* v. *Ideal Steel Supply Corp.*, 126 S. Ct. 1991 (2006). Without the need for reliance, a non-intentional misrepresentation whose culpability is presumed from its materiality can give rise to inequitable conduct even if it is not the "but-for" cause for the examiner's approval of the patent. But even if it were appropriate to punish patentees for *intentional* misrepresentations despite the absence of some showing of causation (and Aventis submits it is not), any rationale for such punishment disappears when the misrepresentation is not shown to be deliberate.

The question presented is extraordinarily important not only to every person and company affected by weak or baseless assertions of inequitable conduct, but also to the effective functioning of our patent system. The proliferation of inequitable conduct charges gives patent applicants strong incentives to inundate the PTO with information in the hopes of forestalling a later inequitable conduct charge. Ironically, this decreases patent quality: Applicants "disclose too much prior art for the PTO to meaningfully consider, and do not explain its significance, all out of fear that to do otherwise risks a claim of inequitable conduct." American Bar Association Section of Intellectual Property Law, A Section White Paper: Agenda for 21st Century Patent Reform 18 (2007).

The information overload resulting from the hundreds of (barely relevant) cited references interferes with efforts to produce higher quality examinations

and contributes to the PTO's record workload crisis. As a recent Director of the PTO has emphasized, the inequitable conduct doctrine "has a perverse effect" on the actions of applicants before the PTO, "discourag[ing] many applicants from conducting a search and lead[ing] others to be indiscriminate in the information they submit." Jon W. Dudas, Testimony before the Committee on the Judiciary, U.S. Senate (June 6, 2007). That "[a]pplicants . . . have an incentive to submit a deluge of information that the [agency] neither wants nor needs, resulting in additional burdens on the [agency's] evaluation of an application," counsels not only against allowing a private right of action for fraud on an agency, as this Court held in *Buckman Co.* v. *Plaintiffs' Legal Committee*, 531 U.S. 341, 351 (2001), but also against allowing inequitable conduct claims to proceed in any but the most extreme cases of fraud and deception.

The ease with which billion-dollar patent rights can be obliterated under the Federal Circuit's weak standard for intent also erodes confidence in the patent system. Property owners value certainty and Congress intended the Federal Circuit to promote that kind of certainty. If the business community loses faith in the enforceability of patents, it is unlikely to continue to invest in research and development, producing a chilling effect on the "progress of the useful arts" that the patent system was meant to promote. The consequences from decreased innovation are especially severe in the pharmaceutical industry, on which the American public depends for disease-curing, life-saving innovations.

In light of these and other considerations, the Federal Circuit's "return[] to the 'plague' of encouraging unwarranted charges of inequitable conduct" (*McKesson Info. Solutions, Inc.* v. *Bridge Med., Inc.*,

487 F.3d 897, 926-27 (Fed. Cir. 2007) (Newman, J., dissenting)), has attracted calls for reform. For example, one national organization advocates limiting the doctrine "to cases where a fraud resulted in the PTO issuing one or more invalidated claims," which is tantamount to the adoption of a "reliance" requirement. American Bar Association Section of Intellectual Property Law, A Section White Paper: Agenda for 21st Century Reform 18 (2007). *See also, e.g.*, Paul M. Janicke, *Do We Really Need So Many Mental and Emotional States in United States Patent Law?*, 8 Tex. Intell. Prop. L.J. 279, 292 (2000) (arguing that the "remedy is worse than the illness" and that, because true inequitable conduct is rare, this does "not seem to justify putting every patentee through the cost and jeopardy of a trial on inequitable conduct").

And, after undertaking a comprehensive review of the patent system, the National Academies of Science and Engineering similarly concluded in 2004 that the costs and uncertainties associated with application of the inequitable conduct doctrine counsel its "elimination" or reform. National Research Council, A Patent System for the 21st Century (2004) at 123, http://www.nap.edu/html/patentsystem/0309089107.pdf. In reaching this conclusion, the Academies singled out for criticism the very standard at issue here: the Federal Circuit's practice of inferring "intent from the materiality of the information that was withheld." *Ibid.*

B. This case, which comes to the Court on final judgment after a bench trial, presents a sound vehicle for shaping the inequitable conduct doctrine. The district court held unenforceable a patent twice granted by the PTO, which provides more than $2 billion in annual revenue. Essential to that holding

was the Federal Circuit's sliding-scale test, and its "should have known" standard for inferring intent from high materiality. Aventis argued that respondents failed to prove the requisite "intent to deceive," including "actual knowledge." App., *infra*, 82a. "Contrary to Aventis' arguments," the district court explained, "it is well-established that proof of actual knowledge is not always necessarily required" to prove intent to deceive; rather, individuals who fail to supply highly material information "should have known" about the information's materiality." *Ibid.* (citation omitted).

The district court also found that *Aventis* failed to prove a credible explanation for the nondisclosure, but the sliding scale was nonetheless essential to its holding. In fact, it is precisely because of the sliding scale that the district court shifted the burden to *Aventis* to prove a credible explanation once high materiality was shown, instead of requiring *respondents* to make a prima facie case of intent. App., *infra*, 87a (finding inequitable conduct because "[t]he elements of nondisclosure and high materiality have been admitted, and no credible excuse demonstrated"); *see also, e.g.*, *Am. Hoist,* 725 F.2d at 1363 (a high showing of materiality "would necessarily create an inference that its nondisclosure was 'wrongful'").

In affirming, the panel majority applied a deferential standard of review and the same sliding scale applied by the district court. No such deference is due, however, should this Court reject the sliding scale. *Koon* v. *United States*, 518 U.S. 81, 100, 116 (1996) ("A district court by definition abuses its discretion when it makes an error of law"). Therefore, this case cleanly presents the legal issue of whether a court may refuse to enforce an otherwise valid pat-

ent based on a finding of inequitable conduct that lowers the intent requirement as the materiality of an omission or misrepresentation increases, effectively permitting a finding of intent to deceive based on nothing more than gross negligence. If the question presented is resolved in Aventis's favor, Aventis will be entitled to judgment on respondents' counterclaim, or, at minimum, to a redetermination of its culpability under the correct standard on remand.

The decision below disregards the careful confines that the Court has imposed on the inequitable conduct doctrine and exacerbates a troubling division of authority that has attracted widespread calls for reform. This Court has repeatedly granted certiorari to adjust the lower courts' expansion of judicially created doctrines. *See Exxon Shipping Co.* v. *Baker*, 128 S. Ct. 2605 (2008); *Stoneridge*, 128 S. Ct. at 761. The inequitable conduct doctrine in patent cases is judge-made in every sense, and can (and should) be shaped by the Judiciary to conform to the broader policies of the Progress Clause and the Patent Act, as well as the general run of federal law. This issue will not benefit from further percolation in the circuits. The split in the lower courts and within the Federal Circuit itself is deep and mature, and the Federal Circuit has exhibited a steadfast unwillingness to revisit the issue en banc. Four decades of confusion are enough. The question presented is ripe—indeed overdue—for this Court's review.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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January 23, 2009

APPENDIX

APPENDIX A

AVENTIS PHARMA S.A. and Aventis Pharmaceuticals, Inc., Plaintiffs–Appellants,

v.

AMPHASTAR PHARMACEUTICALS, INC., Defendant–Appellee,

and

Teva Pharmaceuticals USA, Inc., Defendant–Appellee.

No. 2007–1280.

United States Court of Appeals,

Federal Circuit.

May 14, 2008.

* * *

Donald R. Dunner, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P, of Washington, DC, argued for plaintiffs-appellants. With him on the brief were Allen M. Sokal, Bryan C. Diner, and Esther H. Lim, of Washington, DC, and Michael J. McCabe II, of Atlanta, GA.

Jan P. Weir, Stradling Yocca Carlson & Rauth, of Newport Beach, CA, argued for defendant-appellee Amphastar Pharmaceuticals, Inc. With him on the brief were Steven M. Hanle and Jennifer A. Trusso.

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Meredith Martin Addy, Brinks Hofer Gilson & Lione, of Chicago, IL, for amicus curiae, Sandoz, Inc. With her on the brief were Glen P. Belvis and C. Noel Kaman.

Before RADER, PROST, and MOORE, Circuit Judges.

PROST, Circuit Judge.

This infringement case returns to us for the second time after remand to the district court on the issue of whether Aventis committed inequitable conduct before the United States Patent and Trademark Office ("PTO"). In our earlier opinion, we held that the dosage of the prior art composition used in half-life comparisons with the patented composition was information material to patentability, but we remanded to the district court to determine whether there was an intent to deceive by Aventis in failing to disclose the dosage. After a trial on the matter, the district court found that there was intent to deceive and held the patents unenforceable for inequitable conduct. Because we find no abuse of discretion by the district court in its holding of inequitable conduct, we affirm.

I

Aventis is the owner of U.S. Patent No. RE 38,743 ("the '743 patent") and U.S. Patent No. 5,389,618 ("the '618 patent"), which was surrendered upon the issuance of the '743 Patent. The patents are directed to a composition comprising low

molecular weight heparins ("LMWHs"). Claim 1 of the '618 patent recites:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less than that of heparin and said admixture consisting essentially of
>
> from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons
>
> from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, and
>
> from 60–86% of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,
>
> the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6
>
> said admixture (i) exhibiting a bioavailability and antithrombotic activity greater than heparin and (ii) having an average molecular weight of between approximately 3,500 and 5,500 daltons.

The drug is marketed as Lovenox® in the United States and Clexane® in Europe and is effective in preventing thromboses (blood clotting) while minimizing the possibility of hemorrhaging, especially during high-risk surgery. According to the specification, the advantage of the claimed LMWHs as compared to heparin is that they exhibit a longer half-life, excellent bioavailability, higher rate of absorption, low clearance, resistance to degradation,

increased residence time, and reduced sensitivity to serum factors. '618 patent, col. 2, l. 55–col. 3, l. 26.

A

The prosecution history of the '618 patent is germane to the issue of inequitable conduct. Original claim 1 of the '618 patent application recited as follows:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less that that of heparin and which comprise from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons and from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6.

In the first office action, the patent examiner rejected the claims under 35 U.S.C. §§ 102(b)/103 over several references, including European Patent 40,144 ("EP '144"). The examiner stated that each of the prior art references teaches sulfated heparinic admixtures within the molecular weight ("MW") range of the claims and is considered to be inherently the same as the claimed admixtures. In particular, the examiner explained that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is *identical or nearly identical* to that claimed, it is incumbent

> upon the Applicant to convincingly demonstrate that the claimed product provides some *unexpected or unobvious property* not demonstrated by the prior art products.

(Emphases added).

In response to the office action, Aventis independently addressed the anticipation and obviousness portion of the rejection.[1] With respect to anticipation, Aventis argued that EP '144 does not expressly state that the mixture contains two types of polysaccharides, one with a MW less than 2,000 daltons and one with a MW greater than 8,000 daltons, nor does it state the number average/weight average MW ratio. Presuming, therefore, that the examiner's anticipation rejection rested on inherency, Aventis argued that the evidence in the specification rebuts inherency. In particular, Aventis pointed to example 6 in the specification, which provides in relevant part:

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.
>
> . . . .
>
> (1) From the mixtures produced in Examples 3 and 4:
>
> *40 mg dose:* in 75% of the cases, the half-life was longer than 4 hours, and was even longer

[1] All responses by Aventis were made by its outside counsel, Mr. Robert Schulman.

than *4½ hours in approximately 45% of the cases*;

60 mg dose: in 75% of the cases, the half-life was longer than 3.7 hours.

. . . .

(3) When the product was prepared according to the process described in European Patent *EP 40,144*, the half-life was longer than *4½ hours in 17% of the cases*.

'618 patent, col. 9, ll. 33–58 (emphases added). Example 6 was prepared with the assistance of Dr. André Uzan, a French chemist who was a non-inventor. Based on the example, Aventis argued that the claimed LMWHs exhibit a significantly longer half-life than formulations prepared in accordance with EP '144. Aventis went on to explain that, because it is well established that compounds are inseparable from their properties, the evidence of a difference in a property, i.e., half-life, serves as evidence of a difference in structure. With regard to the obviousness portion of the rejection, Aventis contended that, under 35 U.S.C. § 103, the prior art must suggest the modification to one of skill in the art, yet EP '144 provides absolutely no suggestion to select the particular combination of oligosaccharide chains of specified lengths as claimed.

The examiner was not convinced and issued a second (final) office action, maintaining the prior 102/103 rejection "for the reasons of record in the last Office action." The examiner reiterated that the MW requirements of the claimed compounds are within the range of the compounds disclosed in EP '144 and that any properties would be inherent in the prior

art compounds because they have the same structure as the claimed compounds.[2]

Thereafter, Aventis amended claim 1 to read:

> A heterogeneous intimate admixture of sulfated heparinic polysaccharides, such sulfated polysaccharides having a weight average molecular weight less that that of heparin and said admixture comprising[3]
>
> from 9% to 20% of polysaccharide chains having a molecular weight less than 2,000 daltons
>
> from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, and
>
> from 60–86% of polysaccharide chains having a molecular weight of between 2,000 and 8,000 daltons,

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[2] The examiner also reiterated that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is *identical or nearly identical* to that claimed, it is incumbent upon the Applicant to convincingly demonstrate that the claimed product provides some *unexpected or unobvious property* not demonstrated by the prior art products.

(Emphasis added).

[3] Upon filing a continuing application "comprising" was changed to "consisting essentially of," which is how the claim read when it issued.

> the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6,
>
> said admixture (i) exhibiting a bioavailability and antithrombotic activity greater than heparin and (ii) having an average molecular weight of between approximately 3,500 and 5,500 daltons.

Aventis also submitted a declaration from Dr. Uzan ("first Uzan declaration"). In ¶ 8 of the declaration, Dr. Uzan distinguished the claimed formulations from the formulations in EP '144. First, he noted that the half-life of the claimed formulation is greater than 4½ hours 45% of the time, as compared to the EP '144 formulation which achieved such a half-life only 17% of the time. He remarked, "This represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages." Further, Dr. Uzan stated that he analyzed the EP '144 product and found that 21% of the chains had a MW lower than 2,000; 6% of the chains had a MW greater than 8,000; and 73% of the chains had a MW between 2,000 and 8,000. *Id.* Finally, he concluded that "the formulations of [EP '144] are clearly outside the scope of the present invention." Aventis relied on example 6 and the first Uzan declaration to address the anticipation rejection, arguing that the compounds disclosed in EP '144 are not inherently the same as the claimed compounds because the claimed compounds have a longer half-life and because compounds prepared in accordance with EP '144 fall outside the scope of the claims. With respect to obviousness, Aventis argued that the claimed

compounds are non-obvious over EP '144 because the compositions in EP '144 did not exhibit the unexpected properties of the claimed combination of MW chains.

In the third office action (first office action in the continuing application), the examiner affirmatively withdrew several 102/103 rejections over other prior art references. The examiner continued to reject the claims under 35 U.S.C. § 103 over EP '144 "for the reasons of record in" the second office action. According to the examiner, EP '144 teaches "admixtures of sulfated heparinic polysaccharides having molecular weight ranges which are not patentably distinct from those of the instant claims."[4] The examiner explained that "the instant molecular weight requirements are highly similar to those of the prior art molecular weight ranges," and that no evidence has been presented that the claimed compounds would have "any properties or activities not necessarily inherent [in] the prior art compounds." With respect to the half-life comparisons between the claimed compounds and EP

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[4] The examiner reiterated the statement, in a slightly modified form, that

> the Patent and Trademark Office does not have facilities for testing and comparing various products, and where the prior art teaches a product which is *nearly identical* to that claimed, it is incumbent upon the Applicant to convincingly demonstrate that the claimed product provides some *unexpected or unovbious property* not demonstrated by the prior art products.

(Emphases added).

'144, the examiner stated that the "[a]pplicant has failed to provide evidence that the alleged difference between the half-life of the [EP '144] product and that of the [claimed] mixture is statistically significant." Further, the examiner contended that the first Uzan declaration showed that the differences in composition based on MW were minimal and there was no showing of any unexpected results. Aventis responded by submitting another declaration from Dr. Uzan ("second Uzan declaration"). In ¶ 3 of the declaration, Dr. Uzan referenced five tables comprising the raw data from the half-life comparisons between the claimed compound and the EP '144 compound, which tables were attached to the declaration.[5] Dr. Uzan also provided results from a statistical analysis showing a statistically significant difference between the mean half-life for the claimed compound and that of the EP '144 compound. Specifically, Dr. Uzan reported, "For the claimed compound T½ was 4.36 ± 1.07. For the compound of [EP '144], T½ was 3.33 ± 0.2," and the statistical analysis showed that 4.36 and 3.33 were statistically significant. The mean half-life of 4.36 for the claimed compound was taken from Table X, which indicated the dosage to be 40 mg. The mean half-life of 3.33 for the EP '144 compound was taken from Table III, which did not mention the dosage.

Aventis argued, in its response, that EP '144 does not suggest compounds containing

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[5] Half-life data for the patented compound were contained in Tables I, X, and XI. Half-life data for the EP '144 compound were contained in Tables A and III.

polysaccharides of the claimed MW in the claimed proportions and that the examiner improperly relied on inherency to reject the claimed compounds over EP '144. Referring to the second Uzan declaration, Aventis asserted that different half-lives are obtained with the claimed preparation as compared to the preparation of EP '144. Therefore, Aventis averred, the claimed compounds have been shown to differ from the compounds of EP '144 in both their structure and properties.

Thereafter, the '618 patent application was allowed.

B

Amphastar Pharmaceuticals, Inc. ("Amphastar") and Teva Pharmaceuticals USA, Inc. ("Teva") each filed an Abbreviated New Drug Application ("ANDA") with the FDA to obtain approval to a market generic version of Lovenox®. The ANDA contained a paragraph IV certification challenging the two Aventis patents.

Aventis sued both Teva and Amphastar for infringement of the '618 patent in the United States District Court for the Central District of California. *Aventis Pharma S.A. v. Amphastar Pharms., Inc.*, 390 F. Supp. 2d 936, 938 (C.D. Cal. 2005) ("*Aventis I*"). Amphastar filed a motion for summary judgment on its affirmative defense and counterclaim that the '618 patent is unenforceable due to inequitable conduct. *Id.* at 938–39. Specifically, Amphastar averred that Dr. Uzan engaged in inequitable conduct by failing to disclose that the half-life studies comparing the patented compound to the EP '144 compound were at different doses. *Id.* at 941, 944.

The district court determined that the representation by Aventis that the patented compound had an improved half-life as compared to the EP '144 compound was material to patentability because Aventis referred to the improved half-life at least four times during prosecution and the examiner ultimately allowed the '618 patent application after the final representation that the difference in mean half-life was statistically significant. *Id.* at 950–51. The court found a strong inference of intent to deceive because it could find no credible explanation for comparing half-lives at different doses and because comparisons at the same dose showed little difference in half-life. *Id.* at 951–52. After weighing the evidence of materiality and intent, the court found weighty uncontroverted evidence establishing inequitable conduct. *Id.* at 952. It, therefore, granted summary judgment against Aventis and held the '618 patent unenforceable.[6] *Id.*

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[6] One day prior to issuance of the district court's order, Aventis surrendered the '618 patent to the PTO pursuant to reissue proceedings in the '743 patent application. *Aventis Pharma S.A. v. Amphastar Pharms., Inc.*, 390 F. Supp. 2d 952, 954 (C.D. Cal. 2005). In a subsequent order, the district court granted Aventis's motion to substitute the '743 patent for the '618 patent, and amended its earlier holding of unenforceability to apply also to the '743 patent. *Id.* at 957. In so holding, the district court relied on the well-settled principle articulated in *Hoffman–La Roche Inc. v. Lemmon Co.*, 906 F.2d 684 (Fed. Cir. 1990), that a reissue proceeding cannot rehabilitate a patent held to be unenforceable due to inequitable conduct. *Id.* at 688. Thus, contrary to the assertion by the dissent, op. at 1352, the district court was fully aware of the reissue proceeding, yet recognized

[Footnote continued on next page]

On appeal, Aventis argued that the district court erred in finding materiality because if the dose information were material to patentability, the examiner would have requested it because: she was presented with half-life data that enabled her to compare various doses, Dr. Uzan informed the examiner that the half-life comparison was done at different doses, those of skill in the art frequently compare half-lives at different doses, and half-life is independent of dose. *Aventis Pharma S.A. v. Amphastar Pharms., Inc.*, 176 Fed. Appx. 117, 120 (Fed. Cir. 2006) ("*Aventis II*"). To support the argument that Dr. Uzan informed the examiner that the half-life comparisons were done at different doses, Aventis relied on the statement in the first Uzan declaration that "[t]his represents an increase in 250% in the half life and is very significant because *it enables the same effect to be achieved with lower dosages*," and Dr. Uzan's deposition testimony stating that he believed this to mean "that the comparison is a comparison between two doses of which one is lower than the other." *Id.* at 120–21 (emphasis added) (internal quotations omitted). Aventis relied on this same statement to argue that Dr. Uzan did not intend to deceive the examiner. *Id.* at 123. Aventis further argued lack of intent based on the fact that Dr. Uzan submitted half-life data for the claimed compound at 60 mg, as well as at 40 mg. *Id.*

[Footnote continued from previous page]
that any holding of unenforceability in the original application extended to the reissue application.

With regard to materiality, this court held that it was not plausible to read the statement in the first Uzan declaration as indicating to the examiner that the half-life comparison was done at different doses and, therefore, there was no genuine issue of material fact that Dr. Uzan did not disclose that the comparison was made using data for the two compounds at different doses. *Id.* at 121. We also rejected Aventis's explanation for nondisclosure that using different doses in half-life comparisons was common practice in the field because, in contrast to the references cited in support of this proposition, Aventis did not disclose the actual doses. *Id.* Further, this court did not accept the explanation that the half-life data were dose independent because the evidence clearly suggested otherwise. *Id.* at 121–22. Therefore, we concluded that the withholding of the EP '144 dosage information prevented the examiner from considering information important to patentability and constituted a failure to disclose material information. *Id.* at 122.

While this court found that the dosage of the EP '144 composition was indeed information material to patentability, we held that the district court erred in finding intent to deceive on summary judgment. *Id.* In particular, we held that the reasonableness of the comparison at different doses is relevant to determining whether there was an intent to deceive in withholding the dosage of the EP '144 composition. *Id.* at 122–23. This court reasoned:

> [T]he district court . . . ultimately concluded that the facts supported a strong inference of intent to deceive. The district court's inference was reasonable—by failing to

> disclose that the EP 40,144 data was at a 60 mg dose, Aventis may have been painting the rosiest picture possible as to the half-life improvement of its claimed compounds in an attempt to deceive the examiner. . . . However, there is another reasonable inference—namely, as Aventis argues, if the comparison between different doses was reasonable, the failure to disclose may have been due purely to inadvertence.

Id. at 123. Accordingly, this court reversed the grant of summary judgment of unenforceability of the '618 patent and '743 patent, and remanded to the district court for determination of whether there was intent to deceive. *Id.*

Following remand, the district court held a bench trial limited to the issue of intent. *Aventis Pharma S.A. v. Amphastar Pharms., Inc.*, 475 F. Supp. 2d 970, 975 (C.D. Cal. 2007) ("*Aventis III*"). Thereafter, the court issued its opinion, considering the principle explanations proffered by Aventis for Dr. Uzan's failure to disclose the dose of the EP '144 composition in its half-life comparisons. These explanations were that: (1) comparison of half-lives at different doses was reasonable because it was customary to compare the half-lives of different drugs at the "clinically relevant dose," i.e., the dose presenting the best efficacy-safety ratio, and the half-life comparisons were intended to show a difference in therapeutic properties, not a compositional difference; (2) comparison of half-lives at different doses was reasonable because half-lives are dose independent; and (3) the failure to disclose was due merely to inadvertence. *Id.* at 977–92.

The district court found Dr. Uzan's clinical relevance justification implausible because such a justification presumed a compositional difference between the compounds being compared, yet the issue of inherency was repeatedly raised by the examiner during prosecution. *Id.* at 977–82. The court noted that the examiner recognized that a compound's properties, e.g., half-life, are inherent in its composition and thereby rejected the claims as anticipated by the EP '144 compound under 35 U.S.C. § 102. *Id.* Therefore, the court was not persuaded that Dr. Uzan presented the half-life comparisons to show only a difference in property and not also a difference in composition. *Id.* The court was similarly unpersuaded by Aventis's dose-independence argument because the evidence did not establish that the half-lives were dose-independent, given the high intra-subject variability. *Id.* at 984–86.

Furthermore, the court rejected Dr. Uzan's clinically-relevant dose justification on the grounds that it was incredible because: (1) there was no statistical difference in half-lives when the 60 mg dose of EP '144 composition was compared to the patented composition at a 20 mg, 60 mg or 80 mg dose, i.e., there was a statistical difference only when a 40 mg dose of the patented composition was compared; (2) the '618 patent was not limited to safe and effective doses for particular therapeutic indications; (3) there were a number of preferred therapeutic doses for the patented composition; and (4) Aventis offered no corroborating evidence to support Dr. Uzan's clinically relevant dose justification. *Id.* at 986–89.

Finally, the court declined to find that Dr. Uzan's failure to disclose the difference in doses could be justified based on inadvertence because it was not credible that a scientist with Dr. Uzan's qualifications could have committed, and failed to correct during a lengthy prosecution, such an egregious error, and there was a complete absence of evidence suggesting negligence throughout prosecution. *Id.* at 989–92.

Based on the totality of the facts and circumstances, the court determined that but for Dr. Uzan's intentional omissions, the probability was high that the '618 patent would not have issued. *Id.* at 994. Accordingly, the court held the '618 patent and the '743 patent unenforceable due to inequitable conduct. *Id.*

Aventis appeals the district court's finding of intent to deceive and holding of inequitable conduct. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II

We review a district court's finding of intent to deceive for clear error. *Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1233 (Fed. Cir. 2008); *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed. Cir. 2007). A finding of intent will not be overturned "in the absence of a 'definite and firm conviction' that a mistake has been made." *Hoffmann–LaRoche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1359 (Fed. Cir. 2003) (quoting *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995)). We review the district court's ultimate holding of inequitable conduct for abuse of discretion. *Monsanto*, 514 F.3d at 1233–34; *Cargill*, 476 F.3d at 1365. We will overturn a holding of inequitable

conduct only if it is based on clearly erroneous findings of fact or a misapplication or misinterpretation of relevant law or if the holding evidences a clear error of judgment. *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc in relevant part). Decisions by the district court concerning the admission or exclusion of evidence are reviewed for abuse of discretion. *United States v. Curtin*, 489 F.3d 935, 943 (9th Cir. 2007) (en banc); *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1310 (Fed. Cir. 2006).

"To satisfy the intent to deceive element of inequitable conduct, 'the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive.'" *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1374–75 (Fed. Cir. 2006) (quoting *Kingsdown*, 863 F.2d at 876). Given that direct evidence is often unavailable, intent is generally inferred from surrounding facts and circumstances. *Id.* at 1375. The district court, upon finding materiality and intent, shall "balance the equities to determine whether the patentee has committed inequitable conduct that warrants holding the patent unenforceable." *Id.* (quoting *Monsanto Co. v. Bayer Bioscience N.V.*, 363 F.3d 1235, 1239 (Fed. Cir. 2004)). "The more material the omission or misrepresentation, the less intent that must be shown to elicit a finding of inequitable conduct." *Id.*

III

A

Now, on its second time on appeal, Aventis offers a new justification for Dr. Uzan's failure to disclose

the dosage information in his half-life comparisons.[7] According to Aventis, Dr. Uzan's half-life comparisons were intended to show a difference in properties in response to the obviousness rejection under 35 U.S.C. § 103, not to demonstrate a compositional difference to address the anticipation rejection under 35 U.S.C. § 102, as the district court concluded. Aventis's argument is premised on the fact that while a half life comparison must be done using equivalent doses to establish a compositional difference, a half-life comparison may be done using different doses if the purpose is to establish a difference in property. In fact, Aventis argues, it is more appropriate to use the "clinically relevant dose" of each compound to demonstrate a difference in property.

As a preliminary matter, it appears that Aventis's argument would require us, at least in part, to revisit our prior holding on materiality. The essence of Aventis's argument is that the reason that Dr. Uzan did not disclose the dosage of the prior art compound in his half-life comparisons is that the comparisons were not being used to show a compositional difference and, therefore, the dosage information was not material. We have previously determined, however, that the dosage information

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[7] We note that in its first appeal, Aventis argued only that Dr. Uzan did not have deceptive intent in failing to disclose the dosage information because he thought he informed the examiner that the comparisons were done at different doses, and because he did provide half-life data for the claimed compound at 60 mg as well as at 40 mg. *Aventis II*, 176 Fed. Appx. at 123.

was material to patentability. *Aventis II*, 176 Fed. Appx. at 122. Nevertheless, because materiality and intent to deceive are necessarily intertwined, *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1455 (Fed. Cir. 1984), we will consider the merits of Aventis's argument with respect to deceptive intent.

Aventis contends that the district court made two clearly erroneous findings of fact: (1) that the central question relating to patentability was compositional differences, and (2) that the purpose of Dr. Uzan's half-life comparisons was to show compositional differences. According to Aventis, coursing throughout the district court's opinion is the notion that the central question relating to patentability was compositional differences. During oral argument, Aventis emphasized that the district court referred to compositional differences nineteen times in its opinion. Oral Arg. at 3:9–3:17, *available at* http://www.cafc.uscourts.gov/oralarguments/mp3/2007–1280.mp3. As an example, Aventis quoted the court:

> Thus, the central question throughout the prosecution of the '618 patent was whether the [claimed] and [the] EP '144 LMWH products were compositionally different.

Id. at 10:50–11:03; *see Aventis III*, 475 F. Supp. 2d at 982. Aventis thus contends that the district court erroneously concluded that anticipation was the only rejection of record, even though there was an obviousness rejection present throughout prosecution. Moreover, Aventis asserts that the district court erred in concluding that the "issue of obviousness necessarily folds into, and is subsumed,

by inherency." *Aventis III*, 475 F. Supp. 2d at 982 n.10.

We find nothing in the district court's opinion to suggest that it did not recognize the existence of the obviousness rejection, or that it believed the anticipation rejection to be the *only* rejection of record. Indeed, several statements in the opinion clearly indicate that the court was aware of the obviousness rejection. *Id.* at 980 ("It also relied on [the claimed composition's] properties *to rebut obviousness*."), ("[B]ecause the ratio identified by [the claimed] LMWH exhibited superior properties over EP '144, the inventive formulation could neither be inherent *nor obvious*."), ("This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the [primary examiner's] inherency *and obviousness rejections*.") (emphases added). Although the court incorrectly suggested, in a footnote, that obviousness is subsumed by inherency, we see this as merely a recognition by the court that the notion of inherency was part and parcel of the examiner's rejections. *Id.* at 979. In other words, the properties of a compound are inherent in its composition and, therefore, a difference in property could successfully demonstrate a difference in composition. *Id.* The court understood that, based on the information available to her, the examiner viewed the patented composition and the EP '144 composition to be inherently the same, or nearly the same, and, because the Patent Office did not have the facilities to test the products, the examiner invited Aventis to provide evidence of a difference in property to show a compositional difference. *Id.* at 980; *see In re Best*, 562 F.2d 1252, 1255 (CCPA 1977). We find no clear error in the district court's ultimate conclusion.

Aventis next contends that the district court clearly erred in finding that the purpose of Dr. Uzan's half-life comparison was to show compositional differences to address the anticipation rejection under 35 U.S.C. § 102. Instead, Aventis argues, the MW distribution analysis in the first Uzan declaration, showing a difference between the claimed compounds and those disclosed in EP '144 in the proportion of chains of a given MW, was directed to the anticipation rejection; the half-life comparisons were directed to the obviousness rejection. Further, Aventis contends, Dr. Uzan's statement at the end of the declaration that "the formulations of [EP '144] are outside the scope of the claimed invention," was based on the MW distribution analysis, not the half-life comparisons. According to Aventis, the district court improperly concluded that Aventis could not establish compositional differences with the MW distribution analysis, so it relied instead on the half-life comparisons to show that the compounds were not identical. In support, Aventis quotes the court's opinion:

> But Aventis could not successfully distinguish [the patented compound] merely by appealing to [its] ratio of number average and weight average molecular weights. The EP '144 patent is not limited by a specific ratio of constituents. Rather it employs open claim language "comprising various proportions of particular molecular weight products." Therefore, Aventis attacked sameness based on a difference in properties.

Oral Arg. at 14:21–14:52 (quoting *Aventis III*, 475 F. Supp. 2d at 980).

We cannot agree that the district court clearly erred in its determination that the half-life comparisons were, at least in part, intended to show compositional differences. Nothing in example 6 suggests that the half-life comparison was designed to show only non-obviousness and not lack of identity. The beginning of the example merely states: "This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life." '618 patent, col. 9, ll. 33–35. Moreover, the first Uzan declaration does not clearly delineate between evidence intended to address the anticipation rejection and evidence intended to address the obviousness rejection. All of the evidence directed to the EP '144 reference appears in ¶ 8 of the declaration, without distinction between the § 102 and the § 103 aspects of the rejection, and there is no basis for concluding that the final statement in ¶ 8—Thus, the formulations of [EP '144] are clearly outside the scope of the present invention"—refers only to the MW distribution data and not to the half-life data. We likewise reject Aventis's contention that the court did not recognize that the half-life comparisons were, in part, intended to demonstrate nonobviousness. In fact, immediately following the portion of the opinion quoted by Aventis, the court continued: "It also relied on [the claimed composition's] properties to rebut obviousness." *Aventis III*, 475 F. Supp. 2d at 980. In addition, the court, in reference to a statement by the examiner in the second office action, observed, "This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the [primary examiner's] inherency and obviousness rejections." *Id.* Therefore, we conclude that the district court properly found that the half-life

comparisons were intended to address both the anticipation and obviousness rejections, and, to the extent that they were intended to address the anticipation rejection, the failure to disclose the dosage information evidenced intent to deceive.[8]

Aventis further contends that, in the third office action, the examiner withdrew the § 102 rejection and maintained only the § 103 rejection over EP '144. Yet, Aventis asserts, it was not until the second Uzan declaration, which was submitted after the third office action, that Dr. Uzan provided a statistical analysis showing that the half-life differences were statistically significant. Hence, Aventis urges, the examiner clearly withdrew the § 102 rejection based on the MW distribution data, and the half-life data in the second Uzan declaration was intended only to overcome the § 103 rejection. Aventis thus avers that the district court erred in concluding that the anticipation rejection was still pending at the time of the third office action.

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[8] Aventis further argues that the district court erroneously imputed to Dr. Uzan arguments made by Aventis's attorney, Mr. Schulman, in response to the examiner's rejections. While it is indeed true that Mr. Schulman represented to the examiner that the difference in half-life indicated that the compositions were different, we find nothing to suggest that the district court relied entirely, or in large part, on Mr. Schulman's statements in determining that Dr. Uzan intended to deceive the examiner by his failure to disclose the dosage information in his half-life comparisons. Instead, we find that the court's conclusion rested almost entirely on example 6 of the specification and on the first Uzan declaration.

The court apparently came to the conclusion that the anticipation rejection was still pending because the rejection had not been expressly withdrawn.[9] *Id.* at 982 n.9. Although the court may have erred in concluding that the anticipation rejection was still pending in the third office action, that conclusion was not critical to the court's ultimate determination that there was intent to deceive. In fact, as explained by the court:

> Even if the Court were to accept as true Aventis'[s] unlikely contention that, by the time of Dr. Uzan's Second Declaration, the [primary examiner] had conceded that the [claimed] and EP '144 products were different, there can be no question that inherency was the central, dispositive question up to that point.

Id. at 982. Therefore, even if anticipation were not at issue at the time of the third office action, the court still concluded, based on evidence prior to the third office action, that there was deceptive intent. Any error by the court in concluding that anticipation was still at issue in the third office action does not override the evidence of intent to deceive based on the failure to disclose dosage information in the half-life comparisons in example 6 of the specification and in the first Uzan declaration,

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[9] Notably, the examiner did expressly withdraw other prior art rejections. Also, the examiner stated that the rejection over EP '144 was "repeated for the reasons of record," and reiterated that any properties were considered to be inherent in the prior art compounds, making the record somewhat ambiguous.

both of which were submitted prior to the third office action. We cannot agree that the court clearly erred in its factual findings prior to the third office action and in its determinations with respect to intent to deceive based thereon.

In sum, we find that the district court did not clearly err in determining that the half-life comparisons were, in part, intended to show compositional differences to address the anticipation rejection under 35 U.S.C. § 102 and, therefore, rejecting Aventis's argument that they were intended only to show differences in property, such that dosage information was immaterial.

B

Aventis next argues that the district court clearly erred in excluding evidence that comparison of half-lives at different doses was the standard practice in the LMWH field. The "clinically relevant dose," Aventis avers, is the standard dose for comparison of half-lives, and every contemporaneous publication comparing half-lives did so at the clinically relevant doses, even though those doses may have differed. Aventis contends that Dr. Uzan selected the 40 mg dose for the patented compound and the 60 mg dose for the EP '144 compound because they were the clinically relevant dose. According to Aventis, the 40 mg dose for the patented compound was the approved dose for its most important indication, namely, prevention of deep venous thrombosis ("DVT") during high-risk orthopedic surgery.

The district court excluded the evidence of industry practice because it determined that such evidence was irrelevant to the reasonableness of Dr. Uzan's nondisclosure. *Id.* at 975 n.6. We find no abuse of discretion by the court's exclusion of the

evidence. First, evidence of industry practice of clinically-relevant doses would only be pertinent if there was a finding that the half-life comparisons were used to address obviousness, and not anticipation, because Aventis has conceded that half-life comparison must be at the same dose to show compositional differences. Here, however, the district court found, and we have affirmed, that the half-life comparisons were at least in part intended to show compositional differences to address the anticipation rejection.

Furthermore, the district court, after examining all of the evidence, found it simply incredible that Dr. Uzan selected the clinically relevant doses for his half-life comparisons. In particular, the court noted that neither the claims nor the specification were limited to prevention of DVT in high-risk surgical patients and that the patented composition could be used at several different doses for several different indications;[10] that there was not nearly as

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[10] Aventis disputes this finding by the district court, relying on *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987), for the proposition that a compound need not excel over a prior art compound in all properties to be patentable. However, whether a superior property need be demonstrated throughout the entire claim scope in order to show nonobviousness of a claimed product over a prior art product is a separate question from whether there was deceptive intent in failing to disclose material dosage information in a comparison between the claimed product and the prior art product when there is nothing in the claims or specification to suggest that the dosage of the claimed product was the dosage used for a particular purpose.

significant a difference, or no difference at all, in half-life when any other dose (i.e., 20 mg, 60 mg, or 80 mg) of the patented compound was compared to the 60 mg dose of EP '144; and that there was no evidence corroborating Dr. Uzan's testimony that he selected the 40 mg dose due to its efficacy in preventing DVT.[11] *Id.* at 986–89. Evidence of industry practice using clinically relevant doses would have no impact on the court's credibility determination with respect to whether Dr. Uzan intended the clinically relevant doses in this case.

Therefore, we cannot agree that the district court abused its discretion in excluding evidence that comparison of half-lives at different doses to demonstrate a difference in property was routine practice in the LMWH field.

C

Aventis advances several additional arguments focused on whether Dr. Uzan really had deceptive intent. First, Aventis argues that the court erred in not considering exculpatory testimony by Dr. Uzan indicating that he believed that he informed the examiner that he was comparing half-lives at different doses when he stated, in the first Uzan declaration: "[T]his represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages." This court already concluded in the prior

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[11] The court further noted that the 60 mg dose of the EP '144 composition was the only dose for which there was half-life data available. *Aventis III*, 475 F. Supp. 2d at 984.

appeal, "that there is no genuine issue of material fact that Dr. Uzan did not disclose in this statement that the comparison was made using data from different doses." *Aventis II*, 176 Fed. Appx. at 121. We left open the possibility, however, that Dr. Uzan may have *intended* by this statement to convey to the examiner that the half-life comparisons were done at different doses. *Id.* at 121 n.2. The district court heard Dr. Uzan's testimony and considered it along with all other evidence relevant to deceptive intent, yet determined that it did not outweigh the cumulative evidence evincing an intent to deceive. We cannot find that the district court clearly erred in concluding that other evidence outweighed Dr. Uzan's testimony that he intended by this statement to inform the examiner that the half-life comparisons were done at different doses.

Next, Aventis avers that Dr. Uzan did not fail to disclose the dosage information for the patented compound to the examiner. In example 6, Aventis urges, Dr. Uzan provided half-life data for the patented compound at 60 mg as well as at 40 mg; and, in the second Uzan declaration, he attached the raw half-life data for the patented compound in Table XI, which showed that the half-life of the patented compound was less at a 60 mg dose than at the 40 mg dose that was used in the comparison with the EP '144 compound. Even if we acknowledge that half-life data at other doses for the patented compound were provided to the examiner, the data were provided in a very misleading way. *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1191 (Fed. Cir. 1993) (inference of deceptive intent may arise from misleading character of affidavit); *accord B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1585 (Fed. Cir.

1996). In example 6, half-life data for the patented compound at the 4½ hour cut-off, which could be readily compared to the 4½ hour cut-off data for the EP '144 compound, were only provided at the 40 mg dose. In the first Uzan declaration, reference was made only to the half-life comparison at the 4½ hour cut-off, without reference to the dosage of the patented compound. Moreover, Dr. Uzan failed to disclose, in either example 6 or the first Uzan declaration, the dosage information for the EP '144 compound. Accordingly, we cannot conclude that the district court's finding that Dr. Uzan failed to disclose the dosage information was clearly erroneous.

Lastly, Aventis contends that Dr. Uzan's failure to disclose the dosage information was purely due to inadvertence. In support, Aventis relies on other evidence of inadvertent and benign mistakes made during prosecution of the '618 patent application, suggesting that its omission of the dose of the EP '144 compound was likewise inadvertent. For example, Aventis points out that the first Uzan declaration mistakenly stated that the claimed compound had 1.5% of chains below a specified MW, whereas the remarks by Aventis in its response stated 31.5% of the chains. Here, however, in contrast to any inadvertent omissions made during prosecution, there is sufficient evidence of concealment to warrant a determination that the dose information was intentionally withheld. The fact that Aventis made other inadvertent errors during prosecution has no bearing on this material failure to disclose. Therefore, we cannot agree that the district court clearly erred by not concluding that Dr. Uzan's failure to disclose the dosage information was due to mere inadvertence.

IV

For the foregoing reasons, we affirm the district court's finding of inequitable conduct and holding of unenforceability of the '618 and '743 patents.

AFFIRMED

RADER, Circuit Judge, dissenting.

This court today affirms the unenforceability of a patent due to inequitable conduct. To my eyes, this record does not show clear and convincing evidence of intent to deceive the United States Patent and Trademark Office (USPTO). Moreover, my reading of our case law restricts a finding of inequitable conduct to only the most extreme cases of fraud and deception.

Without doubt, candor and truthful cooperation are essential to an ex parte examination system. With burgeoning application rates, the USPTO must rely on applicant submissions to narrow the prior art search. And, of course, those submissions must be reliable. The threat of inequitable conduct, with its "atomic bomb" remedy of unenforceability, ensures that candor and truthfulness.

Although designed to facilitate USPTO examination, inequitable conduct has taken on a new life as a litigation tactic. The allegation of inequitable conduct opens new avenues of discovery; impugns the integrity of patentee, its counsel, and the patent itself; excludes the prosecuting attorney from trial participation (other than as a witness); and even offers the trial court a way to dispose of a case without the rigors of claim construction and other complex patent doctrines. This court has even

observed a number of cases, such as this one, that arrive on appeal solely on the basis of inequitable conduct where the trial court has apparently elected to try this issue in advance of the issues of infringement and validity. *See, e.g., Frazier v. Roessel Cine Photo Tech, Inc.*, 417 F.3d 1230 (Fed. Cir. 2005); *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co.*, 204 F.3d 1368 (Fed. Cir. 2000).

This phenomenon is not new or unprecedented. At an earlier time, the Federal Circuit also observed that inequitable conduct as a litigation strategy had become a "plague." *Burlington Indus. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988). In response, this court took a case to reduce abuse of inequitable conduct. *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc).

In light of the rejuvenation of the inequitable conduct tactic, this court ought to revisit occasionally its *Kingsdown* opinion. *Kingsdown* claimed a two-piece ostomy device. *Id.* at 869. The examiner rejected claim 50 as indefinite. *Id.* at 870. In response, *Kingsdown* amended claim 50. *Id.* Then, later in the prosecution, *Kingsdown* copied the rejected claim 50, not the amended version, into a continuation application as new claim 43. *Id.* at 870–71. The once rejected, now recopied claim 43 matured into claim 9 of U.S. Patent No. 4,460,363. *Id.* at 871. On the basis of this error that certainly called into question the integrity of the examination system, the district court found inequitable conduct. *Id.* at 871–72. This court, en banc, reversed. *Id.* at 877.

In *Kingsdown*, this court clearly conveyed that the inequitable conduct was not a remedy for every

mistake, blunder, or fault in the patent procurement process. Even mistakes that struck at the heart and integrity of the process—like repeatedly recopying and acquiring rights to a rejected claim—did not amount to inequitable conduct. Instead this court required "culpable" conduct supported by clear and convincing evidence of intent to deceive the USPTO. *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1443 (Fed. Cir. 1991) (*citing Consol. Aluminum Corp. v. Foseco Int'l Ltd.*, 910 F.2d 804, 809 (Fed. Cir. 1990)). At the same time, it is hard to imagine a more material mistake than reasserting claims to rejected subject matter. Materiality of any undisclosed or misleading information, of course, is the other prong of an inequitable conduct analysis. *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1363 (Fed. Cir. 2007). In sum, *Kingsdown* properly made inequitable conduct a rare occurrence.

More recently, however, the judicial process has too often emphasized materiality almost to the exclusion of any analysis of the lofty intent requirement for inequitable conduct. Merging intent and materiality at levels far below the *Kingsdown* rule has revived the inequitable conduct tactic. For example, in *Nilssen v. Osram Sylvania, Inc.*, 504 F.3d 1223 (Fed. Cir. 2007), one of the reasons this court upheld a judgment of unenforceability for an exaggerated claim of small entity status. Nilssen entered into agreements with Philips Electronics North America Corp. ("Philips") to license the patents in suit. *Id.* at 1227–28. Because Phillips had more than 500 employees, the district court found that Nilssen had made several improper small entity maintenance fee payments to the USPTO. *Id.* at 1228. This court affirmed, stating: "[w]e therefore affirm the district court's decision finding that all of

the patents in suit are unenforceable due to inequitable conduct in improperly claiming small entity status." *Id.* at 1233. In *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405 (Fed. Cir. 1994), this court upheld unenforceability under circumstances that are even harder to reconcile with the en banc *Kingsdown* rule. The mistake in that case involved a petition to make special. *Id.* at 1407.

The applicant sought expedited examination of its application on the ground that the claimed invention was being infringed. *Id.* At that time, such a request required an oath or declaration that the applicant made a careful and thorough search of the prior art. *Id.* The applicant submitted that declaration, but later conceded that it actually had only conducted an informal search as opposed to a formal search. *Id.* This process did not result in the issuance of rejected claims, but involved nothing more than an expedited examination. Still this miscarriage rendered the entire patent unenforceable. *Id.* at 1412.

While the case at bar does not feature small entity status or expedited examination, the record still does not, in the context of *Kingsdown*, show a clear and convincing intent to deceive. We are cognizant of the high standard of review. To overturn a discretionary ruling of a district court, the appellant must establish that the ruling is based upon clearly erroneous findings of fact or a misapplication or misinterpretation of applicable law or that the ruling evidences a clear error of judgment. *Kingsdown*, 863 F.2d at 876. While the standard of review is high, it is not insurmountable. Where the district court made clear error of fact, this court must overturn such a determination.

In this case, Dr. Uzan, Associate Director of Biological Research at Aventis, assisted in the prosecution of the application that led to U.S. Patent No. 5,389,618('618) covering a low molecular weight heparin mixture invented by Roger Debrie (Debrie LMWH). Specifically, Dr. Uzan assembled data from various clinical studies comparing the half-lives of the Debrie LMWH to a prior art LMWH invented by Mardiguian (Mardiguian LMWH). Dr. Uzan submitted this data, from the Duchier study and the Foquet study respectively, as example 6 of the patent. In submitting the data, Dr. Uzan did not draw attention to the different doses in those studies.

Without question, Dr. Uzan should have disclosed the dosage of the Mardiguian LMWH in example 6 subsection 3. Unfortunately, the Foquet study chart that Dr. Uzan used did not show the dosage information. Dr. Uzan neglected to add the information. To make it clear, Dr. Uzan did not attempt to conceal data that were otherwise present. Rather he just submitted the study without adding to the disclosure. This omission, even if negligent, is hardly *Kingsdown*'s culpable intent to deceive. Moreover this omission strikes less at the integrity of the system than issuance of a rejected claim, which *Kingsdown* sanctioned.

Likewise, Dr. Uzan ought to have disclosed to the USPTO that he compared the 60 mg dose of the prior art Mardiguian LMWH to the 40 mg dose of the Debrie LMWH in the declaration he submitted on March 29, 1993. Dr. Uzan testified that the different dose "did not come to his mind." In context, this explanation has merit. Dr. Uzan was asked to compare the superior pharmacokinetic properties of the Debrie LMWH over the Mardiguian LMWH prior

art compound. Comparison of drug properties at their clinically relevant (and different) dosages is, of course, completely appropriate. Again, this oversight may have been careless, but hardly culpable. To my eyes, Dr. Uzan's negligence does not rise to the level of intent to deceive, particularly in comparison with *Kingsdown*.

Even a cursory review of example 6 shows no dosage indications. The Debrie LMWH in subsection 1 indicates two dosages. Dosage is an element in subsections 2 and 4 as well. Thus, the absence of a dosage in subsection 3 is blatantly obvious. Surely if Dr. Uzan had intended to deceive the USPTO, he would not have made this omission so conspicuous. Moreover, I find it difficult to fathom that a scientist of Dr. Uzan's caliber and reputation would engage in such deception. As the district court points out, Dr. Uzan has had a magnificent fifty year career with Aventis, has published over 350 scientific articles and has received numerous prestigious awards including the Galien Research Prize, France's highest award for drug discovery. This world-class scientist would hardly risk his reputation and tarnish his brilliant career for a single example in the prosecution of a patent for an invention in which he was not even involved.

The inadvertence in this case presents another difficulty for a finding of intent to deceive. The omissions and prosecution errors were committed by two individuals, Dr. Uzan and Mr. Schulman, Aventis' prosecuting attorney. Collective actions call into question any showing of intent for inequitable conduct. 37 C.F.R. § 1.56 refers to the duty of candor and good faith possessed by "[e]ach *individual* associated with the filing and prosecution of a patent

application." (emphasis added). Mr. Schulman did not know that the doses of the Debrie LMWH and the Mardiguian LMWH were different. Dr. Uzan admitted that he inadvertently neglected to add that information to the graphs. The dosage information was not on the original Foquet chart submitted to the Aventis patent department and Dr. Uzan neglected to add it. Mr. Schulman had no way of knowing that the comparison was at two different doses and therefore the impropriety of using that data to demonstrate compositional difference. Mr. Schulman's arguments also carry the markings of a good faith mistake.

Most important, Dr. Uzan himself revealed the error. This candor is inconsistent with deceptive intent. He submitted all of the underlying data to the patent office with his second declaration on June 9, 1994. Thus, unlike the situation in *Kingsdown*, Dr. Uzan corrected the mistake before it resulted in an issued patent. In Dr. Uzan's second declaration, he clearly articulated that the half-life data showed superior properties of the Debrie LMWH over the prior art Mardiguian LMWH. Still, with all information before the USPTO, the examiner allowed the patent. Lastly, in early 2003, before filing its infringement suit, Aventis filed a reissue application for the '618 patent. The patent reissued on June 14, 2005 with all of the original independent claims, but without example 6. The half-life data were apparently not even necessary for patentability. The USPTO determined that the Debrie LMWH was inventive over the prior art Mardiguian LMWH without relying on the controversial half-life data from example 6.

The USPTO granted the reissue a day before the district court judge granted Teva and Amphastar's summary judgment motion that the '618 patent was unenforceable. Aventis did not have the opportunity to make this argument to the trial judge. This record does not prevent this court, however, from considering all this information in evaluating the inequitable conduct finding. Thus, both materiality and intent seem suspect on this record. In sum, read in the context of *Kingsdown*, I would reverse the district court's determination of inequitable conduct.

APPENDIX B

AVENTIS PHARMA S.A., and Aventis Pharmaceutical, Inc., Plaintiff,

v.

AMPHASTAR PHARMACEUTICALS, INC., and Teva Pharmaceuticals USA, Inc., Defendant.

And Related Counterclaims

Nos. EDCV03 887 MRP PLAX, EDCV04 333 MRP PLAX.

United States District Court, C.D. California

Feb. 8, 2007.

* * *

Donald R. Dunner, Allen M. Sokal, Bryan C. Diner, Esther H. Lim, Finnegan Henderson Farabow Garrett & Dunner, Washington, DC, Michael J. McCabe II, John D. Livingstone, Robert C. Stanley, Finnegan Henderson Farabow Garrett & Dunner, Atlanta, GA, Anthony G. Brazil, Donald L. Ridge, Megan S. Wynne, Morris Polich & Purdy, Los Angeles, CA, for Plaintiffs.

Jan P. Weir, Jennifer A. Trusso, Nicole A. Varner, Steven M. Hanle, Stradling Yocca Carlson & Rauth, Newport Beach, CA, Edith Ramirez, Eugene T. Chen, Lee J. Papageorge, Quinn Emanuel Urquhart Oliver & Hedges, Los Angeles, CA, Francis

C. Lynch, Laurie S. Gill, Goodwin Procter, John T. Bennett, Palmer & Dodge LLP, Boston, MA, for Defendants.

MEMORANDUM OF DECISION FINDING IN FAVOR OF DEFENDANTS AMPHASTAR PHARMACEUTICALS, INC. AND TEVA PHARMACEUTICALS USA, INC. ON THE RELATED ISSUES OF INTENT TO DECEIVE THE PATENT AND TRADEMARK OFFICE AND INEQUITABLE CONDUCT

PFAELZER, District Judge.

I. INTRODUCTION

This case was commenced before District Judge Robert J. Timlin. Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc. (collectively, "Aventis"[1]) brought suit against Amphastar Pharmaceuticals, Inc. ("Amphastar") and Teva Pharmaceuticals USA, Inc. ("Teva") (collectively, "Defendants") for infringement of Aventis' patent, U.S. Patent No. 5,389,618, and its replacement, U.S. Reissue Patent No. 38,743 (collectively, "the '618 patent"). The case was transferred to this Court for all further proceedings on June 27, 2006. A bench trial on inequitable conduct was held December 4 through December 8, 2006. The Court limited its inquiry to Aventis and its agents' intent in failing to disclose

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[1] Pharmuka, Rhone-Poulenc, and Phone-Poulenc Rorer are predecessor corporations to Plaintiff Aventis. At various times, each of these entities was responsible for the enoxaparin product. The Court uses "Aventis" generally to refer to whichever entity was in existence at the time.

highly material information to the United States Patent and Trademark Office ("PTO"). Based on consideration of the evidence adduced at trial and the post-trial arguments made by counsel, the Court concludes as follows:

II. BACKGROUND

Heparin is an anticoagulant used to decrease the clotting ability of the blood. Chemically, it is a heterogeneous mixture of straight-chain anionic mucopolysaccharides having anticoagulant properties. Low molecular weight heparin ("LMWH") is synthesized by various methods of heparin fractionation or depolymerization. These methods break down heparin's long, heavy polysaccharide molecules, yielding smaller, less massive chains in more homogenous proportions. The resulting mixtures consist of shorter chains of polysaccharides having lower average molecular weights.

The '618 patent claims a range of defined LMWH mixtures. These encompass the drug formulation, enoxaparin, approved by the United States Food and Drug Administration ("FDA") as an anticoagulant in diseases featuring venous thromboses. Aventis is the international pharmaceutical company that manufactures enoxaparin, which it markets under the brand name Lovenox®. Enoxaparin was approved in France in 1987. By 1989, it had "taken the French market by storm" and achieved commercial success throughout Europe. Aventis exerted a monopoly position in the European market for enoxaparin in the 1980s by virtue of European Patent 40,144 ("EP '144"), which issued in 1984 and broadly claimed undefined LMWH mixtures invented by J. Mardiguian.

Serious challenges to EP '144 soon threatened this position. Opposition proceedings initiated in the mid-1980s before the European Patent Office to revoke EP '144 as devoid of novelty had, by 1989, proved successful—the opposition was allowed, and the revocation of EP '144 became effective in October 1990. Enoxaparin did not have patent coverage in the U.S. at this time. Aventis had been forced to abandon its U.S. counterpart application to EP '144 in 1984 when it had no argument to oppose the PTO's prior-art rejections. Notwithstanding this deficit, Aventis filed its New Drug Application ("NDA") with the FDA in July 1991 to obtain marketing approval for enoxaparin in the U.S. In concert, Aventis sought to protect enoxaparin in the U.S. with an EP '144 successor: a formulation of enoxaparin invented by Roger Debrie (the "Debrie" or " '618" product).[2] This was the subject of the '618 prosecution. The high cost of FDA approval generated substantial pressure on Aventis to succeed. Internal Aventis documents reveal its commitment of "significant financial and human resources" to the "enoxaparin USA-patent situation."

The '618 prosecution involved successive rounds of rejection and appeal. The Patent Examiner ("PE") issued three Office Actions dated April 2, 1992

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[2] Aventis filed U.S. Patent Application Serial No. 721,315 ("the '315 application") on June 26, 1991 in the PTO, claiming a priority date of June 26, 1990 based upon an earlier French application. On July 16, 1993, Aventis filed a continuation of the '315 application, United States application No. 92,577, which ultimately issued as the '618 patent.

("First Office Action"), October 16, 1992 ("Second Office Action"), and March 2, 1993 ("Third Office Action"). Each rejected the Debrie formulation under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious in light of Mardiguian EP '144. The keystone of Aventis' strategy for overcoming the PE's rejections was to distinguish the Debrie LMWH based on its purportedly superior pharmacokinetic properties—particularly, its longer plasma half-life. The '618 patent discloses that "[t]he processes described in the prior art, and especially in EP '144, do not permit the production of mixtures possessing the requisite pharmacological properties for improved therapeutic applications, namely, a sufficiently long plasma half-life, a fairly high absorption rate, a high bioavailability or alternatively, a low clearance." In support of these assertions, Aventis directed the PE's attention to Example 6 of the '618 patent ("Example 6") and the half-life analysis presented therein.[3]

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[3] Example 6 of the '618 patent provides as follows (emphasis added):

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.
>
> A first pharmacokinetic study was carried out on volunteers between 21 and 30 years of age. Subcutaneous injections of doses ranging from 20 to 80 mg/ml were performed. At intervals of time, samples were drawn (4.5 ml) and stored at approximately 4°C. The samples were then centrifuged for 15 minutes at 2,300 g and

[Footnote continued on next page]

Aventis also submitted two expert declarations from

[Footnote continued from previous page]

the platelet-poor plasma was separated and frozen prior to analysis. The half-life of the mixtures was then determined by measuring the anti-Xa activity. The results obtained were as follows:

(1) From the mixtures produced in Examples 3 and 4:

40 mg dose: in 75% of the cases, the half-life was longer than 4 hours, and was even longer than 4½ hours in approximately 45% of the cases;

60 mg dose: in 75% of the cases, the half-life was longer than 3.7 hours.

(2) *Under identical dosage conditions*, intact heparin injected intravenously possessed a half-life of approximately 0.6 hours.

(3) When the product was prepared according to the process described in European Patent EP 40,144, the half-life was longer than 4½ hours in 17% of the cases.

(4) A second study carried out *under similar conditions* on 20 patients provided the following results for the mixtures according to the present invention:

40 mg dose: in 80% of cases, the half-life was longer than 4 hours, and it was longer than 4½ hours in approximately 40% of the cases;

20 mg dose: in 60% of the cases, the half-life was longer than 3.9 hours.

its employee, French scientist Dr. Andre Uzan ("Dr.Uzan"), who was responsible for the data underlying Example 6.[4]

Throughout the prosecution, Aventis and Dr. Uzan affirmatively represented that Example 6 "clearly demonstrate[d]" a significantly longer plasma half-life for the Debrie LMWH compared to Mardiguian EP '144. At no time, however, did Aventis or Dr. Uzan disclose at what dosage the half-life comparisons in Example 6 had been made. Subparagraph (3) of Example 6 omitted the experimental dose of EP '144. In his Second Declaration, Dr. Uzan presented five tables: Tables I, X, and XI referred to the '618 product, while Tables A and III referred to Mardiguian EP '144. Again, Table III failed to disclose the dose. In fact, Dr. Uzan had compared a *60 mg* dose of Mardiguian EP '144 to a *40 mg* dose of the Debrie product. However, comparing the 60 mg dose amount of Mardiguian EP '144 to the 60 mg dose amount of the Debrie product results in a far closer mean half-life.[5] The difference is not statistically significant.

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[4] The first was submitted on March 29, 1993 ("First Declaration"), the second on May 17, 1994 ("Second Declaration").

[5] This is evident by comparing Table III with Table XI. Table III reported the half-life for Mardiguian EP '144 at a 60 mg dose as 3.33 hours, with a standard deviation of 0.2. Table XI reported the half-life for the '618 product at a 60 mg dose as 3.70 hours, with a standard deviation of 0.82.

III. PRIOR PROCEEDINGS

Amphastar moved for summary judgment on its affirmative defense and counterclaim of inequitable conduct, arguing that Aventis and Dr. Uzan's withholding of the EP '144 dosage constituted a failure to disclose material information to the U.S. PTO and rendered the '618 patent-in-suit unenforceable. Judge Timlin agreed, finding that: (1) the EP '144 dose information was highly material, because Aventis made half-life the centerpiece of its argument for patentability, and a reasonable PE would have considered the experimental dose important in deciding whether to allow Aventis' application on that basis; and (2) the omission of the dose information supported a strong inference of intent to deceive, because the Debrie product's half-life was not significantly different from EP '144 at the same dose. Accordingly, Judge Timlin granted summary judgment in favor of Amphastar and held the '618 patent and the '743 reissue patent unenforceable. *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 390 F. Supp. 2d 936 (C.D. Cal. 2005).

On appeal, the Federal Circuit reversed and remanded, *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 176 Fed. Appx. 117 (Fed. Cir. 2006), concluding that, although there were no genuine issues as to high materiality, a finding of deceptive intent was inappropriate on summary judgment. The panel conceded that Judge Timlin's inference of intent by Aventis to deceive the PTO was "reasonable," observing that "by failing to disclose that the EP 40,144 data was at a 60 mg dose, Aventis may have been painting the rosiest picture possible as to the half-life improvement of its claimed

compounds in an attempt to deceive the examiner." *Aventis*, 176 Fed. Appx. at 123. This concession ratified Amphastar's *prima facie* case of intent. *See Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 984 F.2d 1182, 1192 (Fed. Cir. 1993) ("A party charging inequitable conduct may make a *prima facie* case by showing an unexplained violation of the duty of candor.").

The panel also agreed with Aventis, however. The case for deceptive intent "hinge[d] on an assessment of Dr. Uzan's credibility and an examination of the scientific rationale and facts justifying Dr. Uzan's half-life comparison at different doses." (Fed. Cir. Reply Br. 21-22.) Aventis had stated facts supporting a "plausible justification" for its material omission, but Judge Timlin had denied Dr. Uzan an opportunity to testify to it at trial.

Thus, because "there [was] another reasonable inference [than intent to deceive]—namely, as Aventis argue[d], if the comparison between different doses was reasonable, the failure to disclose may have been partly due to inadvertence"—the finding of intent was premature.

Upon remand and transfer, the Court entertained pre-trial motions,[6] considered the trial

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[6] In the Court's pretrial conference and resultant Minute Order of November 14, 2006, the Court ruled that certain opinions of Aventis' medical expert, Dr. Weitz, regarding the common practice in the industry with respect to doses used to compare LMWHs would be excluded unless Aventis consented to hear certain opinions from Amphastar's patent law expert, Mr. Goolkasian. Aventis agreed not offer expert opinion

[Footnote continued on next page]

briefs of the parties, and conducted the bench trial on intent to which the present decision relates.

IV. LEGAL STANDARD

"Inequitable conduct occurs when a patentee breaches his or her duty of 'candor, good faith, and honesty,'" *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005) (quoting *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995)), by affirmatively misrepresenting or failing to disclose material

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testimony on industry practice from paragraph 2 of Dr. Weitz's supplemental report, and Amphastar agreed not to present Mr. Goolkasian. During the bench trial, however, Aventis repeatedly sought to introduce industry practice testimony through Dr. Uzan. Aventis also sought to avoid its agreement to restrict Dr. Weitz's testimony on industry practice by reference to paragraphs 3 and 4, which are claimed also to deal with industry practice and stand independently of paragraph 2. Amphastar has made a post-trial motion to strike all testimony going to industry practice. The Court finds Aventis agreed with Amphastar to withhold all expert opinion testimony by Dr. Weitz on the *subject matter* of industry practice, regardless of the paragraphs from which that testimony might derive. No other conclusion obviates the need, from Amphastar's perspective, for Mr. Goolkasian's testimony. Dr. Uzan was not covered by Amphastar's agreement. Dr. Uzan was also not a testifying expert under Fed. R. Civ. P. 26(a)(2). He was a percipient fact witness accused of intending to deceive the PTO, and the focal point of the trial. However, the Court finds that the actual practice in LMWHs, even if established, is irrelevant to the reasonableness of Aventis' and Dr. Uzan's non-disclosures in this case. Accordingly, Amphastar's December 4, 2006 motion to strike is denied.

information to the PTO. *Pharmacia Corp. v. Par Pharm., Inc.*, 417 F.3d 1369, 1373 (Fed. Cir. 2005). "The inequitable conduct analysis is performed in two steps comprising 'first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine whether the applicant's conduct is *so culpable* that the patent should be held unenforceable.'" *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362-63 (Fed. Cir. 2003) (emphasis added) (quoting *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1366 (Fed. Cir. 2001)).

The quantum of proof required to show intent is tied to materiality; the "more material the omission or the misrepresentation, the lower the level of intent required to establish inequitable conduct." *Semiconductor Energy Lab. Co., Ltd. v. Samsung Elecs. Co., Ltd.*, 204 F.3d 1368, 1375 (Fed. Cir. 2000). "Materiality does not," however, "presume intent, which is a separate and essential component of inequitable conduct." *GFI, Inc. v. Franklin, Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed. Cir. 1990)). Although "a lesser quantum of proof is needed to establish the requisite intent" in this case, *Aventis Pharma*, 176 Fed. Appx. at 119, Amphastar and Teva must still prove the predicate facts by clear and convincing evidence. *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1187 (Fed. Cir. 2006).

Satisfying this burden does not require "smoking gun" evidence. *Paragon*, 984 F.2d at 1189. The Federal Circuit has "repeatedly said that direct

evidence of intent is unavailable in most cases and unnecessary in any event." *Frazier v. Roessel Cine Photo Tech, Inc.*, 417 F.3d 1230, 1235 (Fed. Cir. 2005); *see also Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs. Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) ("'Intent need not, and rarely can, be proven by direct evidence.'") (quoting *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989)); *Ulead Sys., Inc. v. Lex Computer & Mgmt. Corp.*, 351 F.3d 1139, 1146 (Fed. Cir. 2003) ("[d]irect evidence of deceptive intent is not required"). Rather, "in the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information." *Bruno Indep. Living*, 394 F.3d at 1354; *see also Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1319 (Fed. Cir. 2006) ("Intent...may be inferred from the totality of the evidence."); *Ulead Sys.*, 351 F.3d at 1146 ("deceptive intent is...usually inferred from the patentee's overall conduct"). Such an inference is commonly supported "by a showing of acts the natural consequence of which were presumably intended by the actor." *Paragon*, 984 F.2d at 1189.

Proving intent does not require showing that an individual involved in the prosecution "subjectively believed the [ ] submission was deceptive." *Frazier*, 417 F.3d at 1235-36. It does require that "the involved conduct, viewed in light of all the evidence, including evidence of good faith, [ ] indicate sufficient culpability to require a finding of intent to deceive." *Paragon*, 984 F.2d at 1189 (quoting *Kingsdown Med. Consultants Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc)). Circumstances indicative of good faith must be considered. *Gambro Lundia*

AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1580 (Fed. Cir. 1997). But a "patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997). "[M]erely conclusory statements or completely insupportable, specious or conflicting explanations or excuses will not suffice" to establish good faith, *Paragon*, 984 F.2d at 1190, nor will "[a] mere denial of intent to mislead (which would defeat every effort to establish inequitable conduct)." *GFI*, 265 F.3d at 1275 (quoting *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1416 (Fed. Cir. 1987)). Furthermore, where a patentee "has not proffered a credible explanation for the nondisclosure... an inference of deceptive intent may fairly be drawn in the absence of such an explanation." *Bruno Indep. Living*, 394 F.3d at 1354.

V. THE EXPLANATIONS AND JUSTIFICATIONS OFFERED BY AVENTIS AND DR. UZAN

(A.) The Reasonableness Of Comparing Half-Lives Of LMWHs At Dissimilar Doses.

Aventis contends that Dr. Uzan had scientifically valid reasons for not making his half-life comparison at equivalent doses. Specifically, Aventis contends: (1) that Dr. Uzan used clinical benchmarks derived from scientific literature to select doses for the compounds he compared; (2) that this was the only appropriate method for Dr. Uzan to employ given his objective of comparing the clinical properties of a new drug to an old drug; (3) that it was standard practice in the industry to perform dose-ranging

comparisons when studying the properties of different LMWHs; and (4) that it was reasonable for Dr. Uzan to select a 40 mg experimental dose of the Debrie product because that dose was approved for a use that presented the greatest challenge in terms of balancing safety and efficacy.

Dr. Uzan's testimony was consistent with these contentions. Dr. Uzan testified that his objective in propounding Example 6 was to compare the LMWHs at their "clinically relevant dose[s]," which he defined as the "dose[s] presenting the best efficacy-safety ratio." He clarified that "for the clinicians there is a balance between efficacy and side effects, mainly bleeding, and so the therapeutic dose, clinically relevant, is a dose for which this safety ratio, including bleeding, is the best." According to Dr. Uzan, "[c]omparing the identical dose is not an appropriate comparison" because a "gravimetric comparison ...has no clinical relevance." The reason that a "comparison in the field of heparin is only valued when you compare clinically relevant dose," Dr. Uzan explained:

> is that the low molecular weight heparins are mixtures containing million of saccharides and a very complex composition. And the consequence is that those compounds have, according to this composition, pharmacological, pharmacokinetic, and clinical effects which are composition related. And so clinically it has no sense to compare qualimetric dose... equal quantities, equal amounts in milligram. You cannot do that.

Dr. Uzan further testified to his understanding that, for these reasons, "all the people involved in low molecular heparin compare clinically relevant

dose," and 40 mg was the clinically relevant dose for the indication Dr. Uzan claims to have been focused on—namely, the prevention of deep vein thrombosis ("DVT") in high-risk patients undergoing orthopedic surgery. Dr. Weitz, Aventis' biology expert, testified in support of Dr. Uzan's approach. Although Dr. Weitz condemned Dr. Uzan's failure to identify the Mardiguan EP '144 dose, even suggesting it to have been an unreasonable omission, Dr. Weitz testified that the omission did not affect the validity of Dr. Uzan's half-life comparison. In Dr. Weitz's opinion, Dr. Uzan's "comparison was reasonable because those were the preferred doses of the drugs," and "as clinicians, as doctors, we are only interested in comparing drugs at the doses that have that appropriate benefit-to-risk ratio that—the right efficacy, and the acceptable safety." "As a doctor," Dr. Weitz explained, "I want to know the half-life of a drug at a dose that I am going to use in my patients." Dr. Weitz further testified that "the preferred dose for the high-risk surgical patients [was] 40 mg."

Aventis maintains that Dr. Uzan finds additional support for his clinical justification for selecting 40 mg in scientific articles that compare the pharmacokinetic properties of various LMWHs at their respective—and different—therapeutic doses. Coupled with the fact that no contemporaneous publication studied enoxaparin at 60 mg, Aventis further maintains that these articles prove that Dr. Uzan's clinical rationale comports with the practice of those skilled in the art of LMWHs.

Amphastar and Teva dispute Dr. Uzan and Aventis' contentions, arguing three points: (1) that Dr. Uzan's professed reliance on clinical benchmarks to select an experimental dose is a litigation-inspired

pretext fabricated in order to portray the 40 mg dose as reasonable; (2) that Dr. Uzan and Aventis employed an arbitrary and statistically flawed analytical method in order to cherry-pick the best data and create an artificial impression of significance; and (3) that Aventis adduced insufficient evidence at trial to permit the Court to find any standard practice in the industry to compare LMWHs at their therapeutic, different doses.

It is, however, unnecessary for the Court decide the merits of Amphastar and Teva's particular arguments. Whether selecting the "clinically relevant" dose was scientifically valid given Dr. Uzan's stated objective of comparing the therapeutic properties of a new drug versus an old drug is irrelevant. Whether it is standard practice in the industry of LMWHs to perform dose-ranging comparisons when studying the properties of different LMWHs is irrelevant. Even if the Court accepts both propositions as true, Dr. Uzan's clinical justifications—*as he and Aventis have stated them*—are implausible under the circumstances of the '618 prosecution and, in that context, fail to persuade the Court that the comparison between different doses was reasonable.

At the heart of Aventis' case for reasonableness is the proposition that Dr. Uzan's objective before the PTO was limited to demonstrating that the claimed LMWH, the Debrie '618 formulation, exhibited superior therapeutic properties over a prior art LMWH, the Mardiguian EP '144 formulation, which was known to be compositionally different. The presumption of compositional difference pervades Aventis' case. It was treated as established fact by

every Aventis witness and referenced as such by every Aventis argument.[7] In post-trial briefing, Aventis argued that "it only makes sense to focus on the clinical dose" when the "objective is to compare the clinical properties of a new drug to an old drug." Dr. Uzan himself testified that "[c]omparing the identical dose is not an appropriate comparison, because ... you cannot compare one kilogram of potatoes to one kilogram of mushrooms."

This metaphor reveals that Dr. Uzan presupposed the very conclusion his half-life analysis sought to prove. Certainly, the use of equal weights of potatoes and mushrooms tells you nothing you do not already know about the properties of potatoes and mushrooms; potatoes taste different than mushrooms, no matter how many of either you eat. The problem for Aventis is that the PE was concerned precisely with the open question of compositional difference: had Aventis claimed a potato or a mushroom, and how ought she to tell the difference?

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[7] For example, the objective of each scientific publication Aventis invites the Court to consider for the industry practice was to compare the biochemical properties of various LMWHs known by prior investigation to be compositionally distinct. Similarly, Dr. Weitz testified that his own research involved, and he has himself personally performed, comparisons of the pharmacological properties of different heparin-based products, including enoxaparin, at different experimental doses because those doses were the preferred clinical doses.

(1.) The Central Objection To Patentability Throughout The '618 Prosecution.

In the First Office Action, the PE observed that EP '144 taught the "instantly claimed sulfated heparinic polysaccharide admixture" and relied on an inherency argument in rejecting the Debrie LMWH as anticipated by EP '144. In addition, because the Oestergaard reference taught that LMWH mixtures are "substantially equivalent regardless of the process by which they are obtained," the PE concluded that "it would have been obvious to one of ordinary skill in the art at the time [Debrie invented the '618 product] to select any of the well known prior art methods for obtaining a low molecular weight fraction of heparin for the advantage of increased biological activity."

Aventis responded in two ways, first by defining the composition, then by emphasizing its properties. Aventis stated that "[t]he admixture comprises from 9% to 20% of polysaccharide chains having a molecular weight greater than 2,000 daltons and from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6." Because Mardiguian did not disclose or suggest this particular compositional makeup, and because the properties of LMWHs were said to be highly composition dependent, Aventis argued that Mardiguian did "not permit the production of mixtures possessing the requisite pharmacological properties [to achieve] improved therapeutic applications, namely a sufficiently long plasma half-life." Aventis explained the reason as follows:

> Given the fact that the inventive formulations and those of the European patent exhibit different properties, such as half life, it *necessarily follows that the formulations of the invention could not possibly be the same as those of the European patent.* As is notoriously well established, *compounds and their properties are inseparable* and thus, *when two compounds exhibit different properties it follows that they must necessarily be of different structure.* Here, therefore, it should be apparent that formulations as claimed, having significantly improved half lives as compared to the formulations of the European patent, are necessarily different from those of the European patent.[8] (emphasis added)

Clearly, then, Aventis was well-aware of the PE's concern that the inventive formulation was inherent in EP '144, which is say, that Debrie and EP '144 were essentially the same. But Aventis could not successfully distinguish Debrie merely by appealing to Debrie's ratio of number average and weight

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[8] Aventis argued in closing that Aventis' U.S. patent counsel, Mr. Schulman, went too far here in arguing that the compositions must be different if their properties are different. The Court is at a loss to understand this retreat. It contradicts Dr. Uzan's testimony that the properties of LMWHs are highly composition dependant. More important, if different compositions may not be inferred from different properties, and Aventis could not disprove inherency by virtue of compositional differences alone, then the '618 patent could not be distinguished from EP '144 or overcome the PE's inherency objections.

average molecular weights. The EP '144 patent is not limited by a specific ratio of constituents. Rather, it employs open claim language "comprising various proportions of particular molecular weight products." Therefore, Aventis attacked sameness based on a difference in properties. It also relied on Debrie's properties to rebut obviousness. Foreshadowing Dr. Uzan's trial testimony, Aventis maintained that a LMWH mixture's properties vary with its ratio of chemical constituents, and "the crucial step lies in the selection of the combination of lengths which will provide a final product having the combination of desirable properties." Accordingly, because the ratio identified by Debrie's LMWH exhibited superior properties over EP '144, the inventive formulation could neither be inherent nor obvious.

The PE was not persuaded. In the Second Office Action, she maintained her rejections. The EP '144 LMWH, she wrote, is "inherently the same as" the claimed invention, as its "composition is so close to the instantly claimed admixtures as to be considered the same, or having differences which are within experimental error." Because the PTO lacks "facilities for testing and comparing various products," she noted that it was incumbent on Aventis to "convincingly demonstrate that the claimed product provides some unexpected or unobvious property not demonstrated by the prior art." The PE further noted that the half-life assertions in Example 6 were not convincing because "the *half life for the EP 40144 product appears to be essentially the same as that for the instant mixtures*," and "[n]o statistically significant or convincing data which clearly establishes Applicant's assertions has been provided" (emphasis in original).

This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the PE's inherency and obviousness objections. Aventis relied heavily on Example 6 to respond:

> ...Example 6 of the originally filed application [ ] clearly demonstrates that the preparations of Mardiguian are not inherently the same as those currently claimed. In particular, Example 6 clearly demonstrates that the claimed compounds exhibit improved pharmacokinetic properties and, in particular, the products of the invention were found to have a plasma half-life longer than 4-½ hours in 40-45% of the cases where such half-life was observed in accordance with Mardiguian in only 17% of cases. This represents an increase in 250% in half-life. This is very important for a pharmaceutical because such increased half-life enables use of lower dosages of the preparations in accordance with the invention.

In his First Declaration, Dr. Uzan echoed this position, claiming Example 6 "represents an increase in 250% in half-life and is very significant because it enables the same effect to be achieved with lower dosages."

Aventis also used Dr. Uzan's First Declaration to resurrect its argument that compositional differences themselves, rather than the properties asserted by Aventis to be composition dependent, rendered the Debrie formulation patentably distinct from EP '144. Dr. Uzan recounted the preparation of a LMWH product using the process disclosed by Mardiguian. He claimed that the resulting LMWH had "21% of chains having a molecular weight lower than 2,000;

6% of chains having a molecular weight greater than 8,000 and 73% of chains having a molecular weight between 2,000 and 8,000." Accordingly, Dr. Uzan concluded that "the formulations of Mardiguian [were] clearly outside the scope of the present invention."

The PE remained skeptical. In the Third Office Action, she observed that "the differences in composition between the instant product and the Mardiguian formulation are minimal." Aventis had "failed to demonstrate that such minor differences render the instant invention patentably distinct over the prior art," especially "because [Aventis] ha[d] not provided evidence of any unexpected results." Rejecting Aventis' and Dr. Uzan's respective assertions about the import of Example 6, the PE concluded that Aventis had still:

> ...failed to provide evidence that the alleged difference between the half life of the Mardiguian product and that of the instant mixture is statistically significant. Specifically, with regard to Example 6, [Aventis] states neither the number of volunteers in the first study nor their overall physical condition. No data which clearly and convincingly establishes [Aventis'] assertions in a statistically significant way.

Thus, by this point in the prosecution, the Debrie formulation stood rejected both as anticipated by, and obvious in light of, Mardiguian EP '144. Aventis had yet to successfully rebut either objection. The PE had required Aventis to come forward with clear evidence that the compositions were different, but Aventis' second attempt to prove the Debrie LMWH was chemically distinct from EP '144 based on their

compositional differences had failed. The PE had flagged her willingness to accept evidence of statistically significant differences in pharmacokinetic properties as indirect proof of compositional difference sufficient to disprove inherency, but Aventis had not made the requisite showing.

Aventis argues that by the time of Dr. Uzan's Second Declaration, the PE had acknowledged that the Debrie product was different from EP '144 by dropping her anticipation rejection under 35 U.S.C. § 102. In a Supplemental Response following the Third Office Action, but preceding Dr. Uzan's Second Declaration, Aventis claims that, "as the Patent Office makes only a rejection under 35 U.S.C. § 103 [in the Third Office Action], it is beyond dispute that the Patent Office does not view the claimed preparations as being inherent." Aventis went on: "Indeed, the [First] Declaration previously submitted by applicant refutes such inherency ... [and] ... [i]t being a given, therefore, that the claimed preparations are not inherent, the next questions is whether they would have been obvious ...." In effect, Aventis simply declared victory on inherency and proceeded to argue nonobviousness. This strategic shift is reflected in Dr. Uzan's Second Declaration. Whereas Dr. Uzan repeatedly asserted in his First Declaration that the data presented in Example 6 and elsewhere conclusively established a patentable difference, he interpreted the same data in his Second Declaration solely in terms of the Debrie composition's properties.

There is no need to debate the PE's references to the Patent Act.[9] The Third Office Action explicitly rejects Aventis' attempt to prove its claimed LMWH was chemically distinct from EP '144 based on compositional differences. The PE wrote that "[t]he recited properties of bioavailability and antithrombotic activity are considered to be inherent in the prior art," while "[n]o evidence has been presented which clearly and convincingly demonstrates that the instant compounds would provide any properties or activities not necessarily inherent to the prior art compounds." Moreover, the PE's handwritten Interview Summary Record, dated several months after the Third Office Action, records that "[a]nother declaration will be submitted...to further indicate how the claimed invention distinguishes over the Mardiguian reference." These statements would make little sense if, by this stage, the PE had already concluded that the claimed preparations were not inherent. Thus, the central question throughout the prosecution of the '618 patent was whether the Debrie and Mardiguian EP '144 LMWH products were compositionally different.[10] Even if the Court were to accept as true

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[9] *But see* the Third Office Action, in which the PE restated her rejections over Mardiguian under 35 U.S.C. § 103 without expressly restating them under 35 U.S.C. § 102, but at no time actually withdrew her rejections over Mardiguian under 35 U.S.C. § 102. Not having been withdrawn, those anticipation rejections over Mardiguian were technically still pending. Thus, Aventis' argument based on the PE's citations to the Patent Act is specious.

[10] Here, the issue of obviousness necessarily folds into, and is subsumed, by inherency. Evidence of statistically

[Footnote continued on next page]

Aventis' unlikely contention that, by the time of Dr. Uzan's Second Declaration, the PE had conceded that the Debric and EP '144 products were different, there can be no question that inherency was the central, dispositive question up to that point.

(2.) The Adequacy Of Dr. Uzan's Method For Demonstrating Compositional Difference: Composition-Effect Indistinguishable From Dose-Effect.

Aventis' and Amphastar's experts agreed that, where the objective of a pharmacokinetic analysis is to establish that two LMWH products, or any

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significant differences in pharmacokinetic properties between Debric and EP '144 sufficient to disprove sameness would also be sufficient to prove nonobviousness. In addition, when dealing with LMWHs, the concept of obviousness presents conceptual difficulties. Aventis maintains that a LMWH's ratio between weight average molecular weight and number average molecular weight defines its properties, and the inventive insight comes in recognizing when a specific ratio promises improved therapeutic properties over the prior art. The dilemma arises because, as argued *infra*, a LMWH's therapeutic properties may not always be determinable until the LMWH has been identified as compositionally distinct from the prior art. Obviousness, in such a case, presupposes a determination, one way or another, about inherency. Yet, this may render obviousness impossible in every case: a beneficial property can never be obvious to a person of ordinary skilled in the art when a LMWH is invented if that skilled person cannot know the property is beneficial until after the LMWH is invented. Accordingly, it is more helpful to examine this case through the lens of inherency.

chemical compounds, are compositionally different, a dose-ranging experimental design is inappropriate. The reason is that, if prior experimentation has not conclusively established the two formulations as chemically distinct, any observed differences in pharmacokinetic properties, including half-life, could be explained either by a difference in experimental dose or a difference in the compositions.

Amphastar's pharmacology expert, Dr. Boons, testified that valid experimental design asks one scientific question at a time and keeps all other parameters the same. That way "one can arrive at conclusions whether [the] two preparations have different or the same pharmacokinetic properties." Dr. Boons observed: "[I]f one has two heparinic preparations and one wants to establish that they were not the same, that one is different and has superior properties in this case as measured by anti-X_a activity, one has to keep everything the same except the two preparations. If one then observes a difference, that can then be attributed to the two different preparations."

Aventis' own medical expert, Dr. Weitz, corroborated Dr. Boon's view. When asked on cross examination why he would not want to control all the experimental confounds—or "noise," as he put it—in his experimental design, Dr. Weitz at first hesitated, then responded:

> I mean, I think it depends. If you are trying to compare a pharmacokinetic parameter of two *different* drugs when they are used at the clinically relevant doses, then you don't care about that control [of holding the dose constant]. What you want to do is you want to see what that parameter is at the dose

> that you are going to use in the clinic. (emphasis added)

In other words, Dr. Weitz understood Dr. Uzan's different-dose comparison to be directed at a much narrower scientific question than the PE had actually posed to Aventis and Dr. Uzan. Dr. Weitz testified that Example 6 "wasn't being offered for the purpose of showing that the two drugs were different." Rather, Dr. Weitz understood Example 6 and Dr. Uzan's representations to the PTO about its significance to have been directed at the question whether the half-life of the Debrie product at 40 mg was more effective for the prevention of DVT in patients undergoing high-risk orthopedic surgery than the half-life of the Mardiguian product at 60 mg when used for the same purpose.

Dr. Weitz testified that "there was evidence that [the Debrie and Mardiguian products] were different compositions." For justification, he referred to Dr. Uzan's statement in the First Declaration "that the molecular weight distributions of the claimed product are different from the molecular weight distribution of the prior art product." Dr. Weitz further admitted that his entire testimony was based on this assumption of chemical compositional difference. Therefore, the validity of the testimony of Aventis' sole expert is by his own admission predicated on evidence Dr. Uzan offered to the PE to establish a proposition (compositional difference)

that the PE found insufficient to support that proposition.[11]

Dr. Weitz's testimony is still relevant, however, insofar as it goes to the reasonableness of Dr. Uzan's comparison for the scientific purpose Dr. Uzan was actually making it. When Teva's counsel clarified her question as directed at the intrinsic pharmacokinetic properties of the claimed formulation, not its relative efficacy in the clinic for a particular purpose at a particular dose, Dr. Weitz hesitated again, then retreated:

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[11] Note that the Court is not now considering the question of whether the compositions used in the various studies underlying Example 6 are, in fact, chemically different from each other. Nor is the court concluding whether, as a matter of law before the PTO, Aventis submitted sufficient evidence to establish the same. Rather, the Court makes two observations: (1) because of the chemical nature of LMWHs as heterogeneous mixtures of polysaccharide molecules of varying lengths and weights in defined ratios, the question of compositional difference between two LMWH's is question of law for the PTO—which is to say, the issue is not compositional difference but patentable compositional difference; and (2) whether Dr. Weitz was correct to believe that the Debrie and Mardiguian products are compositionally different, or even that they are in fact patentably compositionally different, is irrelevant. Dr. Weitz's testimony is contingent on the PE's acceptance of Debrie and Mardiguian as patentably compositionally different based on Dr. Uzan's First Declaration. This the PE did not do. Thus, Dr. Weitz's testimony on the reasonableness of Dr. Uzan's comparison at different doses can be disregarded.

> I think if you were trying to show that one product was different in composition from the other, and you want to show whether that difference in composition—you know, whether—sorry. If you want to show that a product is different from another, you might—you might compare them head to head at the same dose.

Even the inventor of the '618 patent, Mr. Debrie, confirmed that a head-to-head comparison is essential when it is the nature and not the uses of a compound being studied.[12]

Accordingly, the Court finds that Dr. Uzan's clinical justification for his different-dose comparison is unreasonable, because Dr. Uzan's experimental design is unconnected to and inconsistent with his true experimental purpose. Aventis cannot disprove sameness broadly with a methodology calculated only to show utility narrowly. Dr. Uzan's comparison cannot show that enoxaparin is compositionally different than Mardiguian at any dose. Nor can it show that enoxaparin, *per se*, as opposed to "enoxaparin–at-40–mg–for-DVT," is superior to

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[12] He testified that "[i]f the tests performed and reported under Subparagraph 3 were not done under the same conditions as those referred to in Paragraph 1, this has no meaning" and "is worthless." Dr. Uzan faults Mr. Debrie for being a chemist who is "not aware about biology," but Mr. Debrie's discipline is immaterial. A professional chemist studying LMWHs certainly knows the importance of holding all parameters constant except the independent variable (the formulation) and the dependant variable (half-life).

Mardiguian, *per se*, as opposed to "Mardiguian–at-60–mg–for-DVT." At best, Dr. Uzan's comparison can illustrate—and the Court here makes no finding that it does—that enoxaparin at 40 mg is superior to Mardiguian EP '144 at 60 mg for preventing DVT in high-risk orthopedic surgery. The uncontrolled, confounding variable of dose renders any more expansive conclusions based on Dr. Uzan's comparison meaningless.

(3.) The Adequacy Of Dr. Uzan's Methodology Presuming Dose–Independence: Uncontrolled Variability.

Aventis argues that because the half-lives of the LMWHs are dose-independent—i.e., as dosage varies, half-life does not vary in a statistically significant way—it was reasonable for Dr. Uzan to select any dose from the Duchier study, from which he drew the 40 mg half-life data for Example 6. However, any composition-effect remains indistinguishable from a possible dose-effect in this case, because the evidence did not establish dose-independence. Aventis never attempted to convince the PTO or argue to the Court on this point, either for the '618 or the EP '144 products. The Duchier study suggests but does not prove dose-independence because, as Dr. Boons reported, a study including a much larger subject group than twelve could reveal statistically significant differences in the mean half-lives between different doses. The Fouquet study, from which Dr. Uzan drew the EP '144 data for Example 6, tested only 60 mg doses of EP '144. As designed, Fouquet was incapable of showing dose-independence of the EP '144 LMWH. Thus, assuming *arguendo* that the Court finds credible Aventis and Dr. Uzan's contention that Dr. Uzan had

no choice but to use 60 mg data for the Mardiguian EP '144 LMWH because the Fouquet study tested only 60 mg doses and that was the only study Dr. Uzan was aware of reporting half-life data for an EP '144 LMWH, it would still not have not have justified Dr. Uzan's belief that the half-life of EP '144 was dose-independent.

This uncertainty rules out a 40 mg to 60 mg comparison; as testified to by Dr. Boons, only a 60 mg to 60 mg comparison could have possibly been reasonable. However, even if the LMWHs do, in fact, have dose-independent half-lives, and even if Dr. Uzan knew this to be true, his dose-ranging comparison was still unreasonable.

(a.) Dose-Independence Of The '618 LMWH. The Duchier study involved measuring the half-life of enoxaparin in 12 individuals at four doses: 20, 40, 60, and 80 mg. In theory, and other things being equal, if the half-life of the '618 enoxaparin was dose-independent, the observed half-lives at each dose should have been virtually identical. Aventis' position is essentially that Dr. Uzan was reasonable in picking the 40 mg dose because dose-independence renders the data from each dose interchangeable. If so, Aventis does not explain how, if 40 mg could be substituted for 60 mg, the half-life improvement over EP '144 was significant at 40 mg but not at 60 mg. The reason is that, in practice, variability between subjects (between the 12 subjects at a given dose) ("inter-subject variability") and variability within each subject (within the four doses tested in every subject) ("intra-subject variability") results in differences in the observed half-life values along Duchier's 20 to 80 mg dose range. Aventis did not give the PE sufficient information to assess the

impact of this variability, a fact about which she complained in the Third Office Action, observing that Aventis "state[d] neither the number of volunteers in the first study nor their overall physical condition."[13]

Although the half-lives exhibited by each of Duchier's subjects along the full 20 to 80 mg dose range were insignificantly different in themselves, they were not interchangeable. The Duchier data revealed a relatively high intra-subject variability. Because the Duchier study used a crossover model, this cannot easily be explained as a subject effect.[14] Rather, the noise within subjects may have been random or caused by uncontrolled factors of which the Court is unaware: e.g., off- or on-protocol differences in the manner or time of the application of the investigational drug, variations in the site of injection, changing medical personnel giving the injection, or behavior changes in individual subjects from one administration to the next. Although the

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[13] In his Second Declaration, Dr. Uzan responded by attempting to reduce the influence of *inter*-subject variability on his comparison. He averaged the half-lives of Duchier's twelve subjects at the 40 mg dose, and, separately, he averaged the half-lives of Fouquet's twelve subjects at the 60 mg dose. It is undisputed, however, that Dr. Uzan, in using only the Duchier 40 mg dose, never accounted for *infra*-subject variability.

[14] This is because intra-subject variability is a function of geno- and phenotypic differences between individuals. Different people respond differently to the same drug; however, without knowing more, the same individuals would not be expected to respond differently to different administrations of the same drug over a short period of time.

slope of this noise was effectively flat across individual subjects, suggesting the absence of a dose effect, it was nevertheless large enough to overwhelm a composition effect when the '618 and EP '144 LMWHs were compared. This explains how, notwithstanding dose-independence, the mean of the 40 mg dose of the '618 product compared to the mean of the 60 mg dose of EP '144 could appear statistically significantly different, while the 60 mg dose of the '618 product did not. Put simply, the noise in the Duchier system swallowed the signal in the Duchier-Mardiguian comparison. Accordingly, even were the half-life of the Debrie enoxaparin dose-independent, Dr. Uzan's different-dose comparison was still incapable of distinguishing between differences in the plasma half-life of the Debrie and Mardiguian products caused by differences in their chemical compositions, as opposed to uncontrolled intra-subject variability.

The experts offered by Amphastar, Teva, and Aventis each advocated different methods by which this intra-subject variability might have been controlled.[15] The Court finds that the methods of

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[15] Dr. Buller favored incorporating all the data points from each of Duchier's twelve subjects at each of the four experiment doses: 20, 40, 60, and 80 mg. Where half-life is independent of dose, the real obstacle to controlling this variability is simply insufficient numbers of observations; thus, Dr. Buller would have used as many observations as were available. Neither Dr. Weitz nor Dr. Boons, by contrast, believe it is necessary or appropriate to consider all the data points; however, if this was to be done, each disagreed with Dr. Buller and favored an alternative method for doing so. Dr. Weitz would determine the mean half-life for each subject by averaging the half-life

[Footnote continued on next page]

Drs. Buller and Boons target and, theoretically, ought to arrive at approximately the same result. Dr. Weitz's method should control intra-subject variance somewhat less well. But, whether Drs. Buller, Boons, or Weitz is ultimately correct is not dispositive, because the problem of intra-subject variability affects experimental efforts to determine the plasma anti-X_a activity and half-life curves of the Mardiguian LMWH just as it does the Debrie enoxaparin.

(b.) Dose-Independence Of The EP '144 LMWH. Even if the EP '144 LMWH was also dose-independent and Dr. Uzan had, in fact, controlled for intrasubject variability in the Duchier data, the reasonableness of Dr. Uzan's methodology does not markedly improve. In Duchier, intra-subject variability was observed across four administrations. In Fouquet, it was unexpressed, because there was only a single administration of EP '144 per subject, but it was no less inherent in Fouquet than Duchier. Had Fouquet made multiple observations of EP '144 in every subject, even at the same dose, the same randomness or hidden confounds creating noise in the Duchier data may well have produced variable half-life values across observations within Fouquet's subjects. At that point, any of the methods proposed

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[Footnote continued from previous page]
values observed along the full dose range and then taking the mean of those means. Dr. Boons, on the other hand, would weight the means of each subject's observed half-life along the dose range according to the standard deviations of those means, which attempts to account for the variability within each subject.

by the experts in this case could have been used to control this variability and increase confidence that any statistically significant differences in half-life observed when the '618 and EP '144 products were compared were signal, not noise, and could therefore be offered as valid indirect evidence of compositional difference between the LMWH products. Fouquet did not make multiple observations, however, and given the specter of unknown, unexpressed, and uncontrolled noise in the Fouquet data that the Duchier data raises, Dr. Uzan's total reliance on the Fouquet study would still have prevented the PE from separating signal from noise.

Thus, under the most favorable assumptions for Aventis possible, it may well have been scientifically impossible for Aventis to clearly and convincingly demonstrate compositional difference. To be certain, controlling intra-subject variability in the Duchier data might have been Aventis' best option for convincing the PTO of non-inherency. The PE may even have deemed this sufficient, notwithstanding the lingering worry about Fouquet. But there is still no dispute: both studies suffer from intra-subject variability, and Dr. Uzan compared them without even attempting to control the noise in the Duchier data, rendering his analysis all the more unreasonable.

(B.) The Credibility Of Dr. Uzan's Clinical–Relevance Justification.

Aventis does not dispute that there is no statistically significant difference between the two compounds' half-lives at the same dose (60 mg). Nor does it contest that there was no statistical difference between Debrie at 20 mg and 80 mg versus EP '144 at 60 mg. *Only the 40 mg dose showed a statistically*

significant difference over EP '144. This gives rise to the natural inference that Aventis sought to achieve by hindsight the appearance of a statistically significant difference where none actually existed; that Aventis and Dr. Uzan engaged in a post-hoc analysis of the Duchier data, "cherry-picked" the one dose permitting a favorable comparison to Mardiguian, and developed in retrospect an analytical framework within which the use of this dose could be rationalized. Even if the Court is mistaken and a comparison at dissimilar doses is in some way scientifically capable of addressing inherency, the reasonableness of Dr. Uzan's comparison also depends on the credibility of his clinical-relevance justification. If it is credible, Dr. Uzan's use of the only dose showing a difference in half-life is reasonable under the clinical relevance model only if 40 mg was the only clinically relevant dose. The evidence does not establish that it was.

First, clinical efficacy was rarely, if ever, the endpoint of Dr. Uzan's work. Dr. Uzan was not a practicing medical doctor regularly engaged in clinical research with human subjects. He testified to being a "pharmacologist and a biologist" primarily engaged in preclinical animal studies using rabbits and "*in vitro* test[s]."

Second, the '618 patent was not limited to the safe and effective doses for particular therapeutic indications. Claim 1 claims a chemical composition broadly. The '618 patent represents that beneficial properties, including a "sufficiently long plasma half-life, a fairly high absorption rate, a high bioavailability or, alternatively, a low clearance," inhere in the claimed composition *per se*, not according to clinical usage. It also represents that

"the mixtures thereby obtained have a favorable ratio of the fractions of high to those of low molecular weights, which endows them with the requisite antithrombotic properties with but slight risk of hemorrhagic effect." Yet, Dr. Uzan's clinical rationale for the use of the 40 mg dose relies on unsafe and "excessive bleeding" caused by the 60 mg dose. Further, the title of the patent itself covers both treatment and prevention: "Mixtures of Particular LMW Heparinic Polysaccharides for the Prophylaxis/Treatment of Acute Thrombotic Events." Nowhere does the patent disclose that the claimed compound is unsafe or not useful at certain doses or for any of its claimed (or possible) indications.

Aventis maintains that it is irrelevant to Dr. Uzan's intent that the '618 patent covers all doses and indications other than the prevention of DVT in high-risk surgery, arguing that Dr. Uzan need not have been concerned with indications approved after he prepared Example 6 because his subsequent declarations merely "fleshed out that original comparison." This ignores the broad coverage of the '618 patent, fails to recognize that future approvals for additional indications were eminently foreseeable, and ignores the fact that Dr. Uzan's duty of disclosure extended not only through the filing of his First and Second Declarations, but throughout the '618 patent's entire prosecution history. *See Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990); *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 34 F. Supp. 2d 1208, 1211 n.1 (C.D. Cal. 1998).

Aventis also contends that Dr. Uzan's focus on the "single breakthrough use of [its] new product" legitimately supported patentability, citing *In re*

Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987), for the proposition that "[t]o be patentable, a compound need not excel over prior art compounds in all common properties." *Chupp* is inapposite. *Chupp* involved a claimed compound that exhibited superior herbicidal activity on only some of the crops with which it could be used. The Federal Circuit held that evidence of this unexpectedly but selectively superior performance was sufficient to rebut a *prima facie* case of obviousness. In this case, anticipation/inherency are at issue as much or more than obviousness. More substantively, although Dr. Weitz testified that the "big advance" enoxaparin "provided was in the high-risk patients, the patients undergoing orthopedic surgery," he described this as "a big advance over unfractionated heparin." Yet, whether the '618 patent was a breakthrough over the EP '144 prior art was the question before the PE. Under *Chupp*, Aventis could secure a patent on a LMWH even if that LMWH was only superior to the prior art in certain properties at certain doses for certain indications. But Aventis' reliance on *Chupp* begs the question of whether the '618 LMWH is, in fact, superior to the EP '144 LMWH prior art *in any property* at *any dose* for *any indication*—and is sufficiently so to prove both compositional difference and nonobviousness. The evidence suggests that only a same-dose comparison could have answered that question.

Because the '618 LMWH was not a breakthrough in preventing DVT in high-risk patients undergoing orthopedic surgery as compared to the prior art LMWHs that were blocking patentability, Dr. Uzan's exclusive focus on this indication is that much harder to explain and impossible to justify. Dr. Uzan's entire clinical-relevance rationale begins to

collapse with evidence that there were a variety of preferred therapeutic doses at the time, depending on the indication. The record reflects, for example: (1) that a 20 mg dose was approved in France in 1987 for prophylaxis in general surgical patients; (2) that a twice-daily 30 mg dose for prophylaxis in high-risk surgical patients was commonly known to be under investigation in North America in the early 1990s, and it secured formal approval in 1993; (3) that a treatment dose of 1 mg/kg—or 80 mg/175 lbs—was approved in France in 1991[16]; and (4) that a 20 mg dose had been approved in 1987 in France for the prevention of DVT in general and orthopedic surgery. It is implausible that an animal biologist attempting to prove compositional difference focused on the clinical dose for an indication nowhere mentioned prior to trial to support a patent broader than this indication because the claimed invention was a breakthrough over a drug not blocking patentability.

Finally, Aventis offered no corroborating evidence of Dr. Uzan's clinical-relevance justification whatsoever. Neither the '315 application nor any document submitted to the PTO during the prosecution of the '618 patent anywhere refers to the concepts of "preferred therapeutic dose," "clinically relevant dose," or prophylaxis of DVT in high-risk orthopedic surgery. Aventis also did not offer the testimony of a single percipient witness to verify Dr.

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[16] There can be no question that Dr. Uzan knew, at least, of the 1 mg/kg treatment dose; he himself authored the toxicology and pharmacology reports in 1990 supporting its approval.

Uzan's account.[17] The Court cannot escape the conclusion that Dr. Uzan's clinical-relevance justification for the Debrie 40 mg dose may find no corroboration because it cannot *be* corroborated, and Dr. Uzan's reliance on it may not have predated the present litigation.

(C.) The Implausibility Of Inadvertence.

Amphastar and Teva having established a *prima facie* case of intent, it fell to Aventis to come forward with facts supporting a plausible explanation or excuse justifying Aventis and Dr. Uzan's highly material omissions. The Federal Circuit tied the reasonableness of Dr. Uzan's comparison to Dr. Uzan's excuse of inadvertence. It held evidence of the former would be probative of the latter. This is

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[17] The record establishes that patent agents, Michelle Morvan and Phillipe Becker, and their supervisor in the Aventis Patent Department, Jacques Savina, were involved in the '618 prosecution. Ms. Morvan was the Aventis Patent Department's heparin expert and the patent agent then in charge of heparin-based products. Mr. Becker drafted the French application which formed the basis for the '618 patent, and the evidence suggests he may have been the true author of Dr. Uzan's First Declaration. Ms. Morvan and Mr. Becker were both involved to differing degrees in documenting Mr. Debrie's alleged invention, drafting the '315 application, and prosecuting the '618 patent. Similarly, Mr. Savina was the head of the patent department with direct supervisory responsibility for the enoxaparin file. Each testified during their depositions that they failed to recall a single relevant detail concerning the prosecution history: not about Example 6; not about the doses used in the Fouquet study; not about the First or Second Declaration; and not about the half-life comparisons stressed to the PE.

why trial testimony dealt so extensively with the science behind Dr. Uzan's analysis: because even "gross negligence is not, in and of itself, sufficient to satisfy the intent element of inequitable conduct." *Ulead Sys.*, 351 F.3d at 1148. Because Dr. Uzan's testimony cannot explain his comparison as reasonable, the Court can now only look to Dr. Uzan's naked assertion that his failure to disclose the Mardiguian dose was inadvertent. He claims that the Mardiguian dose "did not come in [his] mind," that its omission was "pure inadvertence," and Aventis argues that inadvertence amounts to gross negligence, which cannot justify an inference of intent under *Kingsdown*. *See* 863 F.2d at 876.

However, a bare declaration of gross negligence cannot evidence a lack of intent to mislead. *Paragon*, 984 F.2d at 1191; *Univ. of W. Va. v. Vanvoorhies*, 278 F.3d 1288, 1299 (Fed. Cir. 2002). Dr. Uzan has done little more than make a conclusory denial in a pleading. Certainly, if Dr. Uzan's failures of disclosure were unintentional, they could be nothing else but grossly negligent. But for the Court to find that Dr. Uzan's omissions were based on gross negligence, it must be plausible under the facts and circumstances of this case that Dr. Uzan could, in fact, have been grossly negligent. It is not—entirely the opposite.

(1.) The Impressive Qualifications Of Dr. Uzan.

Aventis contends that Dr. Uzan is a world-class scientific mind whose reputation is wholly inconsistent with deceptive intent. The Court agrees that he is a world-class scientist but finds this fact irrelevant to his intent. Dr. Uzan's reputation is wholly inconsistent, not with deceptive intent, but

with negligence—especially negligence of the magnitude that would have had to have been committed here. The evidence shows that Dr. Uzan received training in numerous scientific fields, including but not limited to biological chemistry, coprology, parasitology, serology, hematology, microbiology, physiology, and Human Biological Research. The evidence reflects his current membership in numerous professional organizations, including but not limited to the French Society of Therapeutic and Clinical Pharmacology, France's National Academy of Pharmacy and Society of Biological Chemistry, the International Society of Biochemical Pharmacology, the American Society for Neurosciences, the European Neuroscience Association, the British Pharmacological Society, and The New York Academy of Sciences. Dr. Uzan is also a former member of France's National Center for Scientific Research Commission No. 25. In his nearly fifty-year history with Aventis, Dr. Uzan has published, by his count, over 350 scientific articles, received frequent appointments as an expert, including by the Paris Court of Appeals, and held at least four separate CEO or Director-level posts in the company. In 1983, he received the International Prix Galien, an internationally recognized award within the pharmaceutical industry recognizing innovation in drug discovery.

In addition, Dr. Uzan testified to having been recently elevated to the grade of Légion d'honneur, or Knight of the Honor Légion, by France's President, Jacques Chirac. Dr. Uzan explained that admittance is the highest honor in France, one conferred for outstanding achievements that improve the image of France domestically or abroad.

(2.) What Dr. Uzan Knew, Must Have Known, And Should Have Known.

Unsupported by more, it simply is not credible that a scientist of Dr. Uzan's caliber and distinction could have committed—and then repeatedly failed to correct over such a long period of time—errors as egregious as those in the '618 prosecution. The prosecution history of the '618 patent unambiguously reflects that evidence of a difference in properties sufficient to prove compositional difference and overcome the PE's inherency objections (and, necessarily, her obviousness objections, as well) was Dr. Uzan's goal. It is inconceivable that this fact was unclear to Dr. Uzan. The language of his First Declaration involves multiple assertions of compositional difference, and in it, Dr. Uzan declares his familiarity with the Second Office Action, which expressly rejected the '618 LMWH as anticipated by Mardiguian, stating that Aventis had not shown "any patentable distinction" between the two, and that the '618 product's claimed properties were "inherent since the prior art compounds [were] considered the same." The Second Declaration's abrupt shift in tone away from the language of difference supports the inference that Dr. Uzan was kept aware of the PTO's evolving objections throughout the prosecution. It also demonstrates that Dr. Uzan knew the problem of insufficient proof of statistical significance was among those objections. Moreover, cases from *Ferring* to *Critikon* to *Brasseler* acknowledge that the Court may consider what he who failed to supply highly material information should have known about the

information's materiality.[18] Even a deeply conservative account of what Dr. Uzan should have known must include knowledge of the PE's central objection to patentability. After all, Aventis can scarcely disagree that Dr. Uzan ought to have been aware of the nature of the questions he was called on to answer before the PTO.

Yet, Dr. Uzan still compared the half-lives of the '618 and EP '144 LMWH's at different doses. At trial, he admitted to doing this knowingly. (*See* 12/4 Tr. 85:8-86:19; 143:8-11.) Because Dr. Uzan must (and should) have known what experimental question he was answering, and because Dr. Uzan clearly did know what experimental design he was using to do so, it is inconceivable that a scientist of Dr. Uzan's abilities could have simply overlooked the fundamental scientific mismatch between what his comparison was required to show, to satisfy the PTO, and what it could show, scientifically. Dr. Uzan had no way of knowing if the EP '144 LMWH possessed a

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[18] Contrary to Aventis' arguments, it is well-established that proof of actual knowledge is not always necessarily required. *See Ferring*, 437 F.3d at 1191 (holding summary judgment on intent is appropriate where, among other things, "the applicant knew or should have known of the materiality of the information" not disclosed); *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1376 (Fed. Cir. 2001) ("intent may be inferred where a patent applicant knew, or should have known, that withheld information could be material to the PTO's consideration of the patent application"); *Critikon*, 120 F.3d at 1256-57 (holding that a patentee's failure to appreciate the legal significance of the facts that it failed to disclose did not absolve it of its duty to disclose).

dose-independent half-life. His asserted subjective belief that the '618 product was so possessed was based on too few observations to be reliable. If either or both LMWHs do not, Dr. Uzan's comparison of half-lives at different doses is logically and statistically incapable of proving compositional difference. What is more, since it cannot distinguish a composition-effect from a dose-effect, his comparison is incapable of proving anything at all about the relative half-lives of the '618 and EP '144 LMWHs, *per se*, despite the claim of the '618 patent to enoxaparin, *per se*. Even if the EP '144 and '618 LMWHs do, in fact, have dose-independent half-lives, Dr. Uzan's experimental design is no less handicapped, as it fails to control for high, random intra-subject variability in the Duchier data, and it ignores the risk of uncontrollable intra-subject variability lying dormant in the Fouquet data.

Notwithstanding such weaknesses, Dr. Uzan represented in his declarations to the PTO, in essence, that the claimed LMWH exhibited, at any dose, a statistically significant increase in half-life over the Mardiguian LMWH, at any dose. He further represented that this would enable the use of lower doses in the clinic compared to Mardiguian, and that it proved the Mardiguian LMWH was different from the '618 LMWH. Put simply, Dr. Uzan knowingly gave the PE a narrow answer to her broad question, and then represented that in so doing he had answered her question broadly. It strains credulity to suggest that a scientist of Dr. Uzan's skills and experience could have relied on logic so flawed purely by accident. That a figure such as Dr. Uzan also could have inadvertently failed to notice his error and taken steps to cure it over five

years of involvement in the '618 prosecution is difficult for the Court to accept.

(3.) The Absence Of Clues To Negligence.

Had it truly been inadvertence causing Dr. Uzan's unreasonable comparison and related misstatements, the Court would expect to see clues to his negligence throughout the prosecution. Yet, virtually no red flags appear in the relevant history.[19] At no time did Aventis or Dr. Uzan disclose any fact to the PTO even *reflecting* that a 60 mg dose of the Mardiguian EP '144 LMWH was compared, or that a dose-ranging comparison had been made. Aventis' own expert testified that this was a scientifically unreasonable omission. His view is confirmed by every publication Aventis invites the Court to consider for the industry practice; each one fully discloses what doses are under investigation. Indeed, the Court would be most surprised if a single

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[19] Aventis argues that the submission of the Duchier study's 60 mg dosage information for the Debrie formulation was such a flag to the PE. This argument is of no moment. While the inclusion of Duchier data for two doses in subparagraph (1) might have spurred the PE to ask what dose was used in subparagraphs (2) and (3), Aventis' led the PE away from any inclination to do so by stating that both the 60 mg and the 40 mg dose in subparagraph (1) involved 75% of subjects exhibiting half-lives above four hours, thereby conveying the erroneous impression of practical equivalence between the 60 mg and 40 mg Duchier doses and irrelevance of dose to the comparison to EP '144. Moreover, as the Federal Circuit reasoned, the inclusion of this data might militate toward a finding of intent because it shows Dr. Uzan was aware of the importance of the 60 mg dose.

article among Dr. Uzan's threehundred-plus publications survived peer review without extensive description of its experimental protocol and analytical methods, in addition to the inclusion of the basic summary statistics omitted from the First Declaration.

Aventis and Dr. Uzan also failed to disclose or represent to the PTO: (1) that the single-dose Fouquet study was the sole source of available data on the EP '144 LMWH; (2) that a dose-ranging analysis was used; (3) that Dr. Uzan's exclusive analytical focus was on the prevention of DVT in high-risk patients undergoing orthopedic surgery; (4) that Dr. Uzan selected his experimental dose of the '618 LMWH because it was the "preferred therapeutic dose" or the "clinically relevant dose" for that indication; (5) that the half-lives of the Debrie and Mardiguian products were believed to be dose-independent; or (6) that Example 6 was a not a well-controlled prospective trial, but a meta-analysis comparing data from three different studies performed for three different purposes at three different times, each more than four years before the filing of the patent application. Had Aventis or Dr. Uzan disclosed even one of these facts, it may well have ignited the PE's suspicion, increasing the probability that Dr. Uzan's flawed, dose-ranging study design would have been exposed. Had they all been stated, Dr. Uzan's gross negligence excuse could be viewed more credibly. Where, as here, *none* surfaced anywhere in the application, declarations, or written arguments, inadvertence is simply implausible. Consistently omitting so many references involves the application of diligence, not the commission of negligence.

In summary, the purpose of trying the issue of Dr. Uzan's intent was to afford Aventis the opportunity to substantiate factually the reasonableness of any excuse that Aventis claims for Dr. Uzan's material omissions. The state of the record in this regard is much improved over summary judgment. First, Defendants have clearly and convincingly established that Dr. Uzan's comparison at dissimilar doses was scientifically unreasonable. It could not prove anything the PE wanted to know. Second, Dr. Uzan's clinical-relevance justification did not withstand scrutiny. Dr. Uzan tested a clinically relevant dose for an important indication; however, 40 mg was not enoxaparin's only clinically relevant dose; the prevention of DVT was not its only important indication; and, in any event, the patent's reach was never limited by dose or indication. Third, other things being equal, the errors of omission in the '618 prosecution were errors that a "Dr. Uzan" simply would not have made. They were too egregious, too obvious, and too consistently committed over too long a period of time. The Court may not presume for Aventis' benefit that Dr. Uzan committed uncharacteristic errors of omission that concealed, purely coincidentally, experimental design mistakes that Dr. Uzan's training, skills, and experience strongly suggest he could have never accidentally made, but which were essential for him to make if Aventis was to overcome the PTO's objections to patentability.

VI. THE FACTS AND CIRCUMSTANCES SURROUNDING AVENTIS AND DR. UZAN'S FAILURE TO DISCLOSE MATERIAL INFORMATION

A *prima facie* case of deceptive intent has already been made. A strong inference that Dr. Uzan intended to deceive is reasonable. This is law of the case established by two prior courts. Having rejected Dr. Uzan's excuses, the Court need not revisit it a third time. Nevertheless, because affirmatively proving intent is a burden that must lie with Amphastar and Teva at all times, the Court now separately finds that clear and convincing evidence adduced at trial independently reestablishes—and substantially strengthens—those earlier inferences of intent.

(A.) Clear And Convincing Evidence of Intent To Deceive.

(1.) The Elements Of Intent: Knowledge, Knowledge of Materiality, and No Credible Excuse.

A finding of deceptive intent is legitimate under the Federal Circuit's recent opinion in *Ferring*, 437 F.3d at 1191, because Defendants presented clear and convincing evidence that "there has been a failure to supply highly material information and [ ] the record establishes that (1) the applicant knew of the information; (2) the applicant knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding." *See also Bruno Indep. Living*, 394 F.3d at 1354; *Critikon, Inc.*, 120 F.3d at 1257. The elements of nondisclosure and high materiality have been admitted, and no credible excuse demonstrated. Regarding knowledge, there is

no debate that Dr. Uzan knew the doses used in the Duchier and Fouquet studies, and at trial, Dr. Uzan admitted to knowing that he was comparing the half-lives of the '618 and EP '144 LMWHs at different doses. Regarding knowledge of materiality, it was obvious that a reasonable PE would have considered dosage important. Depending on the dose tested, compositional difference was either possible to prove, or it was not; the difference in half-life either appeared significant, or it did not. Dosage was the fulcrum on which Aventis' entire case for patentability turned.

(2.) Dr. Uzan's Explanation: A Total Absence Of Indicia Of Credibility.

Here, the Court does not rely only on formal, mechanistic criteria to infer intent. Rather, the Court will step back and examine the overall credibility of Dr. Uzan's story on Dr. Uzan's terms—asking: Is it complete? Is it consistent? Is it corroborated? Is it plausible? Is it explanatory? The Court's finding of deceptive intent is entailed by the negative answers it is forced to give for each question on the facts presented. Dr. Uzan's explanation suffers from a total absence of indicia of credibility. Where excusing a knowing nondisclosure of material information depends on believing a justificatory explanation that is coherent only if a sequence of statements are each true, and the evidence does not justify belief in the truth of *any* of those statements, then belief in the truth of the explanation cannot be justified. The Court is presented with just such a case. Believing Dr. Uzan's explanation requires the Court to accept, at a minimum, that Dr. Uzan was concerned with clinical relevance; that he was focused on DVT; that 40 mg was the therapeutically

preferred dose; that Fouquet was the only known source of EP '144 data[20]; that the half-lives of the '618 and EP '144 LMWHs were dose-independent; that Dr. Uzan did not know, nor should he have known, that the PE's primary argument against patentability was based on inherency; that he subjectively believed the '618 and EP '144 LMWHs to be compositionally distinct; that it was mere coincidence that Dr. Uzan's methodology specifically called for the only dose of the '618 LMWH reflecting a statistically significant difference in half-life; that Dr. Uzan's omission of the EP '144 dosage information in Example 6 was inadvertent; that his omission of the EP '144 dosage information in Table III of the Second Declaration was inadvertent; and that the total absence, prior to litigation, of any reference to the DVT indication, to any scarcity of sources of EP '144 data, or to the concepts of clinical relevance of dose, therapeutically preferred dose, or dose-independence of half-life was also coincidence. That not one of these propositions is credible individually renders Dr. Uzan's explanation not credible globally.

(B.) Conclusion.

Negligence played no role in Aventis and Dr. Uzan's failure to disclose the EP '144 dose information. This is evident from the magnitude of

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[20] This is improbable considering that enoxaparin as claimed and disclosed by the EP '144 patent had been widely prescribed in Europe prior to the '618 prosecution and studied in human volunteers as early as 1983. It was also disclosed in the 1989 Annual Report that clinical trials were ongoing in the United States.

the coincidence necessary to explain, as purely accidental, the convergence of Dr. Uzan's mistakenly narrow focus on clinical relevance; with his mistakenly narrow focus on DVT in high-risk orthopedics; with the memory loss of the Aventis Patent Department regarding both; with the incorporation of the only dataset supportive of patentability, into a flawed experimental design calculated to answer a question not asked; with the repeated omission over time, by both Aventis and Dr. Uzan separately, of precisely those bits of information capable, if disclosed, of arousing the PE's suspicions as to the negligence; with the consequent issuance of an urgently needed patent on a commercially valuable drug which has been argued, though not yet proven, to be chemically indistinct from unpatentable prior art.

This is a case involving a statistical analysis designed post-hoc and rationalized in hindsight to fit a hoped-for result. Legally and practically, Dr. Uzan stands before the Court in the same position as he would if no evidence of subjective good faith had been offered. Therefore, based on the totality of the facts and circumstances surrounding Dr. Uzan's repeated omissions, the Court hereby finds the Defendants have shown by clear and convincing evidence that Dr. Uzan intended to deceive the PTO.

VII. DISPOSITION

At this point, the Court must determine "whether the material misrepresentations or omissions in question are sufficiently serious in the light of the evidence of intent to deceive, to warrant the severe sanction of holding the patent unenforceable." *Hoffmann—La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1372 (Fed. Cir.

2003). Balanced against the Federal Circuit's recognition of high materiality, the requisite showing of intent is proportionally less. *See Bristol—Myers Squibb Co. v. Rhone—Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed. Cir. 2003). The Court need not be detained by intricate questions of weight. But for Dr. Uzan's intentional omissions, the probability is high that the '618 patent would not have issued. The '618 patent must therefore be found to be unenforceable on the ground of inequitable conduct.

ACCORDINGLY, IT IS ORDERED:

(1.) United States Patent No. 5,389,618, and its replacement, United States Reissue Patent No. 38,743, are unenforceable by virtue of inequitable conduct before the U.S. PTO.

(2.) Defendant Amphastar Pharmaceuticals, Inc.'s MOTION TO STRIKE IMPROPER EXPERT OPINION TESTIMONY BY ANDRE UZAN is DENIED.

APPENDIX C

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2007-1280

AVENTIS PHARMA S.A. and AVENTIS PHARMACEUTICALS, INC.,

Plaintiffs-Appellants,

v.

AMPHASTAR PHARMACEUTICALS, INC.,

Defendant-Appellee,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

Appeal from the United States District Court for the Central District of California in case no. 03-CV-887, Senior Judge Mariana R. Pfaelzer.

O R D E R

NOTE: This order is nonprecedential

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellants,* and a response thereto having been invited by the court and filed by the Appellees, and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on October 2, 2008.

FOR THE COURT
/s/

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* Amici Curiae, Pharmaceutical Research and Manufacturers of America; Group of Interested Patent Law Professors; 3M Company, et al.; Biotechnology Industry Organization; Johnson & Johnson; and Generic Pharmaceutical Association were granted leave to file briefs in support of the Appellants' combined petition for panel rehearing and for rehearing en banc.

Jan Horbaly
Clerk

Dated: 09/25/2008

cc: Donald R. Dunner
Jan P. Weir, Frances C. Lynch
Counsel for Amici Curiae

FILED
U.S. Court of Appeals
for
the Federal Circuit
SEP 25, 2008
JAN HORBALY
CLERK

AVENTIS PHARMA V AMPHASTAR PHARM, 2007-1280 (DCT-03-CV-887)

APPENDIX D

UNITED STATES COURT OF APPEALS, FEDERAL CIRCUIT

AVENTIS PHARMA S.A. and Aventis Pharmaceuticals Inc., Plaintiffs-Appellants,

v.

AMPHASTAR PHARMACEUTICALS, INC., Defendant-Appellee,

and

Teva Pharmaceuticals USA, Inc., Defendant-Appellee.

No. 05-1513.

April 10, 2006.
Rehearing and Rehearing En Banc Denied June 7, 2006.

Before RADER, SCHALL, and PROST, Circuit Judges.

PROST, Circuit Judge.

Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc., (collectively, "Aventis") appeal from decisions of the United States District Court for the Central District of California granting summary judgment in favor of Amphastar Pharmaceuticals, Inc., ("Amphastar") and Teva Pharmaceuticals USA, Inc., ("Teva") (jointly "appellees") holding unenforceable United States Patent No. 5,389,618

("the '618 patent"), *Aventis Pharma S.A. v. Amphastar Pharm.*, 390 F.Supp.2d 936 (C.D. Cal. 2005) ("*Aventis Opinion*"), and United States Reissue Patent No. 38,743 ("the '743 reissue patent"), *Aventis Pharma S.A. v. Amphastar Pharm.*, 390 F.Supp.2d 952 (C.D. Cal. 2005). Although there are no genuine issues of material fact with respect to materiality, because genuine issues of material fact remain as to intent, we *reverse* the district court's grant of summary judgment of inequitable conduct and *remand* for further proceedings consistent with this opinion.

BACKGROUND

The '618 patent and the '743 reissue patent disclose and claim mixtures of low molecular weight herapin ("LMWH") used to prevent blood clots. During prosecution of the application leading to the '618 patent and the '743 reissue patent, Aventis compared the half-life of a product allegedly covered by the '618 patent (Example 6 of the '618 patent or "Debrie LMWH") at a 40 mg dose to the half-life of a prior art product ("EP 40,144 LMWH" or "Mardiguian LMWH") at a 60 mg dose. Aventis made these comparisons to the Patent and Trademark Office ("PTO") in the patent application, in several office action responses, and in two declarations by a French scientist named Dr. Andre Uzan to show an unexpected and significantly better half-life of Debrie LMWH when compared to EP 40,144 LMWH. Aventis did not, however, expressly disclose the dosages at which the half-life comparisons were made, and specifically, that the EP 40,144 LMWH data was for a 60 mg dose.

The '618 patent and the '743 reissue patent purportedly cover drug compositions called Lovenox®

that are approved by the Food and Drug Administration ("FDA"). Amphastar and Teva filed Abbreviated New Drug Applications ("ANDAs") with the FDA to obtain approval to market generic versions of Lovenox®. In response, Aventis, the owners of the '618 patent and the '743 reissue patent, filed a patent infringement suit against Amphastar and Teva in the United States District Court for the Central District of California.

The district court granted a motion for summary judgment of unenforceability due to inequitable conduct submitted by Amphastar. Without holding a hearing, the court concluded that Aventis's repeated representations of patentability based on the purported improved half-life of Debrie LMWH were material. The court faulted Aventis for comparing data based on different doses to show an improved half-life, when a comparison of available data using the same doses actually showed that there was little if any difference between the half-lives of the prior art and the purported invention. The court rejected Aventis's argument that Dr. Uzan's first declaration can reasonably be interpreted as meaning that the disclosed half-life data was based on different dosages, calling the argument "specious."

Regarding intent, the court rejected Aventis's argument that the use of the 40 mg Debrie LMWH data, as opposed to the 60 mg Debrie LMWH data, was reasonable. The court stated that the question is not whether use of the 40 mg data was reasonable, but whether there was an omission of material fact, particularly in light of the fact that the same study showed that the 60 mg Debrie LMWH data and the 60 mg EP 40,144 LMWH data was much closer than the 40 mg Debrie LMWH data and the 60 mg EP

40,144 LMWH data. Based on these circumstances, the court found that the facts support a strong inference of intent. The court then weighed materiality and intent. It found weighty uncontroverted evidence sufficient to establish materiality and intent to deceive, and further stated that Aventis submitted just a scintilla of evidence in opposition. It therefore granted summary judgment of unenforceability due to inequitable conduct.[1] Aventis timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a) (1).

DISCUSSION

A. Standards of Review

We review a district court's grant of summary judgment under the law of the applicable regional circuit. *CollegeNet Inc. v. ApplyYourself Inc.*, 418 F.3d 1225, 1230 (Fed. Cir. 2005). In the Ninth

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[1] Aventis filed the reissue application that led to the '743 reissue patent before filing suit against Amphastar and Teva. During prosecution of the reissue application, Aventis informed the examiner that it was not relying on any statement or argument based on Example 6 made during prosecution of the application leading to the '618 patent. The '743 reissue patent issued, and therefore Aventis surrendered the '618 patent by operation of law, the day before the district court granted Amphastar's summary judgment motion with respect to the '618 patent. After granting summary judgment on the '618 patent, the court applied the holding of *Hoffman-La Roche Inc. v. Lemmon Co.*, 906 F.2d 684, 688-89 (Fed. Cir. 1990) (inequitable conduct in original patent renders any reissue patent unenforceable), to enter summary judgment of unenforceability against the '743 reissue patent. *Aventis Pharma*, 390 F.Supp.2d at 954-55.

Circuit, a grant of summary judgment is reviewed de novo. *Leonel v. Am. Airlines, Inc.*, 400 F.3d 702, 708 (9th Cir. 2005). "We must determine 'whether, viewing the evidence in the light most favorable to the nonmoving party, there are any genuine issues of material fact and whether the district court correctly applied the relevant substantive law.'" *Id.* (quoting *Lopez v. Smith*, 203 F.3d 1122, 1131 (9th Cir. 2000) (en banc)).

This court recently stated the standards for finding inequitable conduct as follows:

> Applicants for patents have a duty to prosecute patents in the PTO with candor and good faith, including a duty to disclose information known to the applicants to be material to patentability. A breach of this duty may constitute inequitable conduct, which can arise from an affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive or mislead the PTO. A party asserting that a patent is unenforceable due to inequitable conduct must prove materiality and intent by clear and convincing evidence. Once threshold findings of materiality and intent are established, the trial court must weigh them to determine whether the equities warrant a conclusion that inequitable conduct occurred. This requires a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent. In

> contrast, the less material the information, the greater the proof must be.

Purdue Pharma L.P. v. Endo Pharm., Inc., 438 F.3d 1123, 1128-29 (Fed. Cir. 2006) (citations omitted).

B. Materiality

We first consider whether there is any issue of material fact that the applicant for the '618 patent failed to disclose material facts to the PTO. The threshold showing of materiality required to proceed to the "balancing" portion of the inequitable conduct inquiry can be met by showing a reasonable examiner would have considered such information important in deciding whether to allow the application. *Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1316 (Fed. Cir. 2006).

The district court first determined that "Amphastar, by clear and convincing evidence, has met its initial burden of identifying for the court those portions of the materials on file that it believes demonstrates the absence of any genuine issue of material fact with respect to Aventis's failure to disclose material information." *Aventis Opinion*, 390 F.Supp.2d at 946. We agree that based on Aventis's undisputed omissions, Amphastar met its initial burden of showing that Aventis failed to disclose material information. Aventis never disclosed during prosecution that it derived the half-life data for the EP 40,144 LMWH at a 60 mg dose. The half-life comparisons were highly material to patentability. In multiple office actions, the examiner rejected claims for the Debrie compounds based on the EP 40,144 patent. Each time, Aventis distinguished the Debrie compounds based on their "significant" increase in half-life over the EP 40,144 compounds without providing any information

regarding the dosage at which the data for either compound was obtained. In its final office action, Aventis provided three tables of test data: 1) Debrie LMWHs labeled as obtained at 40 mg; 2) Debrie LMWH labeled as obtained at 60 mg; and 3) EP 40,144 LMWH without a label as to its dosage. The failure to disclose that the EP 40,144 data was obtained at 60 mg denied the examiner an opportunity to determine whether the differences in half-lives between the Debrie and EP 40,144 compounds were significant. Therefore, an omission that would have revealed that the difference in half-lives was actually much smaller was material to patentability. A comparison made at the same dosage, 60 mg, would have yielded a much smaller difference in half-life. Given the centrality of the differences in half-lives to patentability, by failing to disclose the dosage of the 60 mg compound or to disclose that the difference in half-lives at the same dosage was actually lower, Aventis failed to disclose material information to the PTO.

The district court then found that Aventis failed to establish any facts showing a genuine issue of material fact that a material omission was made in prosecution of the '618 patent. *Id.* at 946.

On appeal, Aventis argues that it has raised material facts regarding materiality of the omission. Aventis contends that if the dose information was material, the examiner would have requested it because 1) she was presented with half-life data that enabled her to compare various doses, and 2) she had a motivation to compare them. Aventis argues that the examiner would have been so motivated because Dr. Uzan did inform the examiner that the dosage comparison was done at different dosages, Dr. Uzan

never expressly represented that he was comparing half-life at the same dose, those of skill in the art frequently compared half-lives at different doses and so the examiner should have assumed this here, and because the specification teaches that the half-life of the claimed products are independent of dose. We reject these arguments.

In support of its argument that Dr. Uzan did inform the examiner that the dosage comparison was done at different dosages, Aventis points to language in Dr. Uzan's March 29, 1993 declaration, stating:

> the claimed formulations had a plasma half life longer than 4 1/2 hours in 45% of the cases in contrast to Mardiguan [sic] who achieved such a half life in only 17% of the cases. This represents an increase in 250% in the half life and is very significant because *it enables the same effect to be achieved with lower dosages.*

(J.A. 1894) (emphasis added). Dr. Uzan explained at his deposition that he believes that the second sentence "say[s] that the comparison is a comparison between two doses of which one is lower than the other." (J.A. 2119-20.) Aventis's rebuttal expert claimed the statement "reasonably conveys that at a lower dose of the [Debrie] product, a higher percentage of subjects exhibited a half-life longer than 4 1/2 hours." (J.A. 1010.) Aventis maintains that the court erred in dismissing this interpretation of the sentence as "specious," and argues that, at a minimum, the testimony is subject to reasonable debate.

Although Dr. Uzan may have had some doubt as to the meaning of his statement, we find there is no reasonable debate as to what it stated to the patent

office. A reasonable examiner would understand the statement only to allege a benefit of the claimed invention, not as a disclosure that different dosages were being compared. Aventis's own statements incorporating Dr. Uzan's declaration support this conclusion. For example, in one office action, Aventis stated:

> [T]he half life obtained for the claimed preparation was 4.36 +1.07 hours whereas that for Mardiguian was 3.33 +0.2 hours. This is approximately a 30% difference in results and is significant in that it means that *the claimed preparations can be administered in significantly lower doses.*

(J.A. 1933) (emphasis added); (*see also* J.A. 1885-86 (referencing Dr. Uzan's statement)). It is not plausible to read these statements as indicating to the examiner that the data for the Debrie LMWH was obtained for a lower dose than the Mardiguian LMWH. They tell the examiner that the longer half-life of the claimed invention is a benefit. We therefore agree with the district court that there is no genuine issue of material fact that Dr. Uzan did not disclose in this statement that the comparison was made using data from different doses.[2]

Second, although Aventis did not expressly represent that the half-life comparison was at the same dosage, it repeatedly compared the 40 mg

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[2] If, as Aventis argues, Dr. Uzan did actually believe he was disclosing a comparison of different doses, in part because he is a native French speaker, this may go to his intent, as discussed further below.

Debrie LMWH table's data with the unlabelled EP 40,144 data. By making the comparison at different dosages without disclosing that this was so, Aventis led the examiner away from any questions about dosage or any motivation to question the dosage for the EP 40,144 data.

In addition, we reject Aventis's argument that the examiner would be motivated to compare half-lives at different dosages, as this was common practice. In each of the prior art references Aventis cites as showing comparisons at different dosages, the differences in dosages was expressly disclosed. In addition, although a comparison of preferred therapeutic doses may be the norm, there is no evidence that the examiner was ever made aware that the preferred therapeutic dose for the Debrie compound was 40 mg. Therefore, though it may at times be reasonable to compare half-lives for different dosages would not have motivated the examiner to compare the unlabelled 60 mg EP 40,144 data with the 60 mg Debrie data, when the comparison provided used the 40 mg Debrie data.

Finally, we reject Aventis's position that the examiner would be motivated to compare different dosages because the specification stated that the claimed compounds were dose independent. Indeed, if the examiner truly credited the fact that the Debrie LMWHs are dose independent, the examiner would have had no reason to compare the EP 40,144 data with different doses of the Debrie data because the Debrie data at different doses would be the same. In addition, the examiner could not have been aware of whether the EP 40,144 data was for a particular dose or for some combination of dosages, such that a comparison would be irrelevant.

In summary, it was insufficient to merely submit the underlying data to the examiner and later argue that the examiner could have requested the EP 40,144 dosage information to make additional comparisons. The withholding of the EP 40,144 dosage information prevented the examiner from considering information important in deciding whether to allow the application, and was therefore a failure to disclose material information to the PTO. *Digital Control*, 437 F.3d at 1314.

C. Intent to Deceive the PTO

Even if an omission is found to be material, the omission must also be found to have been made with the intent to deceive. "Materiality does not presume intent, which is a separate and essential component of inequitable conduct." *GFI, Inc. v. Franklin, Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed. Cir. 1990)). To find an intent to deceive, "the involved conduct, viewed in light of all the evidence, including evidence of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1189 (Fed. Cir. 1993) (quoting *Kingsdown Med. Consultants Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc)). "Intent need not be shown by direct evidence, but may be inferred from the totality of the evidence." *Digital Control*, 437 F.3d at 1319. However, "[i]n the summary judgment context, all inferences must be made in favor of the nonmovant; thus, it is often improper to determine at summary judgment that a patentee made intentional misstatements or omissions to the PTO." *Id.* at 1317. On summary judgment, to create a genuine issue of

material fact, Aventis was required to state specific facts supporting a plausible justification or excuse for its failure to disclose material information. *Paragon Podiatry*, 984 F.2d at 1191.

Here, the district court did not find direct evidence of intent to deceive, but found that the "facts and circumstances surrounding the failure to disclose the dose differential ... supports a strong inference of intent by Aventis to deceive the PTO." *Aventis Opinion*, 390 F.Supp.2d at 951-52. Aventis contends that the district court erred in finding an intent to deceive on summary judgment by denying Dr. Uzan an opportunity to testify in person, ignoring evidence negating intent, misconstruing deposition testimony, and drawing factual inferences adverse to Aventis. Because Aventis has met its burden of setting forth a plausible justification for its failure to disclose material information, deciding all inferences in favor of Aventis, we hold that the district court erred in finding intent to deceive on summary judgment.

For example, the district court found it irrelevant whether comparison at different doses was reasonable. *Id.* at 951. On appeal, Teva also advocates this position, arguing that the relevant inquiry is whether there was an intent to deceive in failing to disclose the 60 mg dosage amount of the prior art product. We disagree. The reasonableness of the comparison between different dosages *is* relevant to determining whether the failure to disclose that the comparison was made using 60 mg EP 40,144 data was made with an intent to deceive.

Because there exist genuine issues of material fact as to the reasonableness of the comparisons made by Aventis,[3] we must draw an inference for purposes of summary judgment that it was reasonable to compare the 40 mg Debrie half-life with the 60 mg EP 40,144 half-life. Accepting that inference, the district court was required to determine whether Aventis still intended to deceive by withholding the dosages at which the comparisons were made.

Aventis maintains that Dr. Uzan had a reasonable belief that he informed the examiner that his half-life comparison was made at different doses and that he could not have intended to deceive because he disclosed the data based on 60 mg. Aventis further explains that Dr. Uzan had no reason to make a prospective statement about what would be possible using a lower dose based on a comparison at the same dose, because he could and did directly make that point by comparing the 60 mg EP 40,144 LMWH data against the 40 mg Debrie LMWH data. Aventis also points out that the district court did not even reference, let alone draw reasonable inferences from the fact that Dr. Uzan submitted the half-life data for 60 mg of Debrie LMWH, which would allow the examiner to compare the data from equal doses.

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[3] For example, Aventis argues the comparison was reasonable because: 1) it reflects the preferred dosage level for therapeutic reasons; 2) the 60 mg dosage level was not preferred because it caused bleeding in some patients; and 3) the 40 mg dosage level was more reliable because it had been confirmed in a separate study.

Although the district court did not reference all of Aventis's arguments, it ultimately concluded that the facts supported a strong inference of intent to deceive. The district court's inference was reasonable by failing to disclose that the EP 40,144 data was at a 60 mg dose, Aventis may have been painting the rosiest picture possible as to the half-life improvement of its claimed compounds in an attempt to deceive the examiner.[4] Appellees contend that this is only reasonable inference to draw from the facts presented.

However, there is another reasonable inference-namely, as Aventis argues, if the comparison between different doses was reasonable, the failure to disclose may have been due purely to inadvertence. Based on the facts presented by Aventis, these are not "insupportable, [or] specious ... explanations or excuses." *Paragon Podiatry*, 984 F.2d at 1190. Neither are Aventis's contentions merely "[c]onclusory allegations and attorney arguments." *Ferring v. Barr*, 437 F.3d 1181, 1193 (Fed. Cir. 2006). Aventis presents declarations from the inventor, the declarant, and an expert witness stating facts supporting a "plausible justification" for its material omission. *Paragon Podiatry*, 984 F.2d at 1191. Therefore, a finding of intent was inappropriate on summary judgment.

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[4] Even the disclosure of the 60 mg Debrie data might ultimately militate a finding of intent to deceive because it implies that Dr. Uzan was aware that the 60 mg data was relevant to the comparison, but did not specifically tell the examiner why.

CONCLUSION

While we agree with the district court with regard to its finding of materiality on summary judgment, there remain genuine issues of material fact regarding Aventis's intent to deceive the PTO. Therefore, we reverse the district court's decisions granting summary judgment of unenforceability of the '618 patent and '743 reissue patent and remand for further proceedings consistent with this opinion.

APPENDIX E

United States District Court, C.D. California,
Eastern Division.

AVENTIS PHARMA S.A. and Aventis Pharmaceuticals Inc., Plaintiffs,

v.

AMPHASTAR PHARMACEUTICALS, INC. and Teva Pharmaceuticals USA, Inc., Defendants.
No. EDCV03-887 RT(SGLX), EDCV04-333RT (SGLX).

June 15, 2005.

TIMLIN, District Judge.

The court, Judge Robert J. Timlin, has read and considered defendant Amphastar Pharmaceuticals, Inc. ("Amphastar")'s motion for summary judgment for inequitable conduct pursuant to Federal Rules of Civil Procedure, Rule 56 ("Rule 56"), plaintiffs Aventis Pharma S.A. and Aventis Pharmaceuticals Inc. (collectively, "Aventis") opposition, and Amphastar's reply. Based on such consideration, the court concludes as follows:

I.

BACKGROUND

Aventis is a pharmaceutical company that manufactures Lovenox. Lovenox is a blood thinner that inhibits the formation of certain venous blood clots called thromboses. Lovenox is derived from

heparin. Heparin is a mixture of long polysaccharide molecules obtained from the internal organs of animals such as pigs and cattle. Through a chemical process, heparin's longer molecules can be broken down into shorter molecules. A group of these shorter molecules are called low molecular weight heparins ("LMWHs"). U.S. Patent No. 5,389,618 ("the '618 patent") covers a range of defined LMWHs, including Lovenox, and their administration to patients who are susceptible to blood clots.

Aventis filed an action in this court against Amphastar and Teva Pharmaceuticals USA, Inc. ("Teva") (collectively, "Defendants") for infringement of the '618 patent. Defendants dispute infringement and claim that the '618 patent is invalid and unenforceable. One of Amphastar's grounds for unenforceability is the affirmative defense and counterclaim of inequitable conduct by Aventis.

Amphastar now moves the court for summary judgment on its affirmative defense and counterclaim that the '618 patent is unenforceable due to Aventis' inequitable conduct.

II.

UNCONTROVERTED MATERIAL FACTS

The following are uncontroverted material facts supported by admissible evidence:

> On May 8, 1981, Aventis filed European Patent Application No. 81/400728.2 ("European Patent Application") based upon French Patent Application No. 80/10791 ("French '791 application"). The European

Patent Application was subsequently published on November 18, 1981 as European Patent 40,144.[1]

On June 26, 1990, Aventis filed French Patent Application No. 90/8013 ("French '013 application"), the priority application of the '618 patent. The French '013 application lists the sole inventor as Roger Debrie ("Debrie").

In early 1991, Aventis had begun the process of obtaining drug approval for "Lovenox" in the United States. Aventis had no patent protection for Lovenox in the United States at that time.

In a January 1991 internal memorandum, Aventis acknowledges the lack of and need for patent protection in the United States and notes an April 1991 target deadline for filing its New Drug Application ("NDA").

On June 17, 1991, a month before filing its NDA, in another Aventis' internal memorandum discussing Mardiguian 40,144, Aventis states: "Enoxaparin is not expressly described in this application but is comprised in the claims." The memorandum then notes that the Mardiguian 40,144 patent was revoked and goes on to state, "A patent application concerning the molecular distribution of enoxaparin has been filed on June 26, 1990 in France and must be filed in different countries before June 26, 1991."

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[1] This order will refer to European Patent 40,144 as "Mardiguian 40,144." Mardiguian was the inventor of European Patent 40,144.

On June 26, 1991, Aventis filed United States Patent Application Serial No. 721,315 ("the '315 application") to the United States Patent and Trademark Office ("PTO"), claiming a priority date of June 26, 1990 based upon the French '013 application. Undisputed footnote 5: On July 16, 1993, Aventis filed a continuation of the '315 application, United States application No. 92,577, which ultimately issued as the '618 patent, the patent in suit.[2]

In July 1991, shortly after filing the patent application, Aventis filed its NDA for Lovenox.

In its 1991 NDA submissions, Aventis claimed that the '315 application covered Lovenox.

In 1992, Aventis represented to the PTO that the invention claimed in the '315 application was patentably distinct from Mardiguian 40,144 (which was the same as the French '611 patent).

Aventis distinguished the compositions of Mardiguian 40,144 in the '618 patent's written description.

The '315 application was filed with 28 original claims with original Claim 1 being the only independent claim.

In an Office Action dated April 2, 1992, the PTO rejected all the original claims for various reasons and in particular rejected Claims 1-7 and 24-28 for being anticipated or obvious over several references, including Mardiguian 40,144.

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[2] The '315 application issued as the '618 patent.

On August 3, 1992, Aventis responded to the Office Action by arguing that the prior art did not render the claims unpatentable.

On October 16, 1992, the PTO issued another Office Action rejecting all the pending claims including rejecting Claims 1-7, 24-28, and 29-31 as both anticipated and obvious in view of the prior art including Mardiguian 40,144.

On April 16, 1993, Aventis filed an "Amendment After Final Rejection" responding to the PTO's rejections. In its response, Aventis refers to arguments that were discussed during the interview with the PTO examiner on March 2, 1993.

In support of its April 1993 arguments, Aventis submitted an expert declaration of its employee, Dr. Andre Uzan ("Dr. Uzan") ("First Uzan Declaration"), which specifically addressed the Examiner's statement that the half-life data reported in Example 6 of the '315 application was not significant.

The First Uzan Declaration also includes an analysis of a purported reproduction of Example 8 of Mardiguian 40,144 finding 21% of molecules below 200 daltons, 6% greater than 8,000, and 73% between 2,000 and 8,000, which the declaration states "is clearly outside the scope of the present invention."

On July 16, 1993, Aventis filed a continuation application, which ultimately issued into the '618 patent.

On September 9, 1993, Aventis filed a Preliminary Amendment which amended the claims and responded to the Examiner's May 13, 1993 Advisory Action.

On November 20, 1993, the PTO issued another Office Action once again rejecting the pending claims over Mardiguian 40,144.

On May 16, 1994, Aventis filed another Amendment responding to the Examiner's objections.

After another interview with the Examiner on May 17, 1994, Aventis filed a Supplemental Response dated June 17, 1994 and another Declaration from Dr. Uzan ("Second Uzan Declaration"). This Second Uzan Declaration presented five tables: "Tables, I, X and XI which refer to the compound of the invention and Tables A and III which refer to the compound of Mardiguian."

The Second Uzan Declaration goes on to compare the half-life data in Table X (4.36 hours +/1.07) with the data in Table III (3.33 hours +/.69), and asserts that the difference is statistically significant.

A 1984 Aventis study by Aiach and Fourtillan ("Aiach/Fourtillan Study") is the source of the data in paragraph (3) of Example 6 of the '618 patent (as well as Table III attached to the Second Uzan Declaration filed during the prosecution of the '618 patent).

Aventis acknowledged that paragraph (3) of Example 6 in the '618 patent was "a product prepared according to the process described in European Patent EP 40,144."

In November/December 1985, in connection with Aventis' application for marketing approval in Europe, Aventis prepared a dose-ranging study on

PK 10169[3] by, among others, Frydman/Duchier ("Frydman/Duchier Study"). The Frydman/Duchier dose-ranging study shows a half-life of 4.36 hours +/1.07 for 40 mg dose and 3.70 +/0.82 for 60 mg dose.

The Frydman/Ducheir study is described in Example 6 of the '618 patent, and is the source of the data in paragraph (1) of Example 6 and Tables X and XI in the Second Uzan Declaration. The results of the 1986 Frydman/Duchier Study were published in 1988: Frydman, et al., The Antithrombotic Activity and Pharmacokinetics of Enoxaparine ..., 28 *Journal of Clinical Pharmacology* 609-618 (1988).

The information in the '315 application and the '618 patent regarding the biological properties of the claimed invention and those of prior compounds was provided by Dr. Uzan.

Dr. Uzan testified at his deposition that he recalled the following four sources of the data regarding the biological properties of the claimed invention and those of the prior art compounds: (1) the 1984 Aiach/Fourtillan Study; (2) the 1986 Dawes publication; (3) the 1986 Frydman/Duchier Study (results published in 1988); and (4) a later study referred to in paragraph 4 of Example 6, perhaps attributable to Guibert.

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[3] PK 10169 is a specific LMWH. It is also known as enoxaparin.

III.

ANALYSIS

A. Legal Standard Governing Motion For Summary Judgment

Under Federal Rules of Civil Procedure, Rule 56(c) ("Rule 56(c)"), a district court may grant summary judgment where "the pleadings, depositions, answers to interrogatories, and admissions on file, together with affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law."

The Supreme Court and the Ninth Circuit have established the following standards for consideration of such motions: "If the party moving for summary judgment meets its initial burden of identifying for the court those portions of the materials on file that it believes demonstrates the absence of any genuine issue of material fact," the burden of production then shifts so that "the nonmoving party must set forth, by affidavit or as otherwise provided in Rule 56, 'specific facts showing that there is a genuine issue for trial.'" *T.W. Elec. Serv., Inc. v. Pacific Elec. Contractors Ass'n*, 809 F.2d 626, 630 (9th Cir. 1987) (citations omitted). With respect to these specific facts offered by the non-moving party, the court does not make credibility determinations or weigh conflicting evidence, and is required to draw all inferences in a light most favorable to the non-moving party. *See id.* at 630-31 (citations omitted).

Rule 56(c) nevertheless requires this court to enter summary judgment, "after adequate time for discovery and upon motion, against a party who fails to make a showing sufficient to establish the

existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). The mere existence of a scintilla of evidence in support of the non-moving party's position is insufficient: "[T]here must be evidence on which the jury could reasonably find for the [non-moving party]." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). This court thus applies to either party's motion for summary judgment the same standard as that for a motion for a directed verdict: "[W]hether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." *T.W. Elec. Serv.*, 809 F.2d at 630.

B. Amphastar's Motion

1. Legal Standard for Inequitable Conduct

Amphastar contends the undisputed facts, even with all reasonable inferences in Aventis' favor, establish that Dr. Uzan engaged in inequitable conduct to obtain the '618 patent. Generally, patent applicants owe a "duty of candor and good faith" to the PTO. 37 C.F.R. § 1.56(a); *see also Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995). "A breach of this duty constitutes inequitable conduct." *Id.* Inequitable conduct can render a patent unenforceable. *See Ulead Sys., Inc. v. Lex Computer & Mgmt. Corp.*, 351 F.3d 1139, 1144 (Fed. Cir. 2003).

To render a patent unenforceable, the party asserting inequitable conduct must show (1) affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information; and (2) an

intent to deceive the PTO. *See Molins PLC*, 48 F.3d at 1178 (citing *J.P. Stevens & Co. v. Lex Tex, Ltd.*, 747 F.2d 1553, 1559 (Fed. Cir. 1984), *cert. denied*, 474 U.S. 822, 106 S.Ct. 73, 88 L.Ed.2d 60 (1985)); *Cross Med. Prods. v. Medtronic Sofamor Danek, Inc.*, 2005 U.S. Dist. LEXIS 6545, at *36 (C.D. Cal. 2005). Materiality and intent must be established by clear and convincing evidence. *Ulead Sys., Inc.*, 351 F.3d at 1144. The court then weighs materiality and intent "to determine if equity warrants a finding of inequitable conduct." *Id.*

Inequitable conduct is an equitable doctrine and therefore is not an issue for a jury to decide. *PerSeptive Biosystems, Inc., v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1318 (Fed. Cir. 2000). "Although the premises of inequitable conduct require findings based on all the evidence, a procedure that may preclude summary determination, a motion for summary judgment may be granted when, drawing all reasonable factual inferences in favor of the non-movant, the evidence is such that the non-movant can not [sic] prevail." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 547 (Fed. Cir. 1998).

The issue before the court is whether certain factual representations on behalf of Aventis by Dr. Uzan to the PTO or nondisclosures by him to the PTO concerning the purported improved half-life of the '618 patent over the half-life of Mardiguian 40,144 constitute inequitable conduct.[4]

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[4] Half-life is the time over which the concentration of a drug falls to half of its original concentration in the blood.

2. Relevant Prosecution History of the '618 Patent

The Background of the Invention section of the '618 patent states: "The processes described in the prior art, and especially in EP 40,144, do not permit the production of mixtures possessing the requisite pharmacological properties for improved therapeutic applications, namely, a sufficiently long plasma half-life, a fairly high absorption rate, a high bioavailability or alternatively, a low clearance." It also states that "the mixtures of the ['618 patent] exhibit a half-life longer than other known preparations."(emphasis added).

Aventis supported the half-life assertion with Example 6 of the '618 patent ("Example 6"). Example 6 states:

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.

A first pharmacokinetic study was carried out on volunteers between 21 and 30 years of age. Subcutaneous injections of doses ranging from 20 to 80 mg/ml were performed. At intervals of time, samples were drawn (4.5 ml) and stored at approximately 4[deg] C. The samples were then centrifuged for 15 minutes at 2,300 g and the platelet-poor plasma was separated and frozen prior to analysis. The half-life of the mixtures was then determined by measuring the anti-Xa activity. The results obtained were as follows:

> (1) From the mixtures produced in Examples 3 and 4:[5] 40 mg dose: in 75% of the cases, the half-life was longer than 4 hours, and was even longer than 4 1/2 hours in approximately 45% of the cases; 60 mg dose: in 75% of the cases, the half-life was longer than 3.7 hours.
>
> (2) Under identical dosage conditions, intact heparin injected intravenously possessed a half-life of approximately 0.6 hours.
>
> (3) When the product was prepared according to the process described in European Patent EP 40,144, the half-life was longer than 4 1/2 hours in 17% of the cases.
>
> (4) A second study carried out under similar conditions on 20 patients provided the following results for the mixtures according to the present invention: 40 mg dose: in 80% of cases, the half-life was longer than 4 hours, and it was longer than 4 1/2 hours in approximately 40% of the cases; 20 mg dose: in 60% of the cases, the half-life was longer than 3.9 hours.

A significant portion of the '618 patent's prosecution history focused on Example 6 and its subject: half-life. In an Office Action date April 2, 1992, the PTO rejected all claims of the '618 patent. The Examiner stated that Aventis must "provide[ ] some unexpected or unobvious property not demonstrated

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[5] Examples 3 and 4 illustrate the preparation, properties, and certain structural characteristics of the '618 patent.

by the prior art products." In response, on August 3, 1992, Aventis referred the Examiner to Example 6 and stated, "[i]n this regard, the Examiner is referred to Example 6 of the originally filed application wherein the product was prepared in accordance with the European patent and found to have a half-life significantly shorter than was observed with the formulation of the present invention ... Here, therefore, it should be apparent that formulations as claimed, having significantly improved half-lives as compared to the formulations of the European patent, are necessarily different from those of the European patent."

The Examiner rejected Aventis' response. He wrote, "[a]pplicant's arguments filed August 3, 1992 ... are not deemed to be persuasive .... Applicants assertions regarding the comparative data in the specification (comparison to EP 40144-Mardiguian) are not convincing ... since the half-life for [the Mardiguian patent] appears to be essentially the same as that for the instant mixtures."

On April 16, 1993, Aventis again responded to the Examiner's rejection. Aventis reiterated its position that the '618 patent was patentable over Mardiguian 40,144. Aventis wrote, "[i]n particular, Example 6 clearly demonstrates that the claimed compounds exhibit improved pharmacokinetic properties and, in particular, the products of the invention were found to have a plasma half-life longer than 4-1/2 hours in 40-45% of the cases where such half-life was observed in accordance with Mardiguian in only 17% of the cases. This represents an increase in 250% in half-life."

In support of the April 16, 1993 response, Aventis submitted the First Uzan Declaration. In

addition to reiterating the purported increase in half-life, Dr. Uzan stated, "[t]his represents an increase in 250% in half-life and is very significant because it enables the same effect to be achieved with lower dosages."

On July 16, 1993, Aventis filed a continuation application that ultimately issued as the '618 patent. In the application, Aventis responded to the Examiner's May 19, 1993 Advisory Action. Among other things, Aventis represented, "the data to which applicant presented in the Declaration Pursuant to 37 C.F.R. § 1.132 have a high degree of accuracy."

On November 20, 1993, the Examiner responded. He stated that Aventis "has failed to provide evidence that the alleged difference between the half-life of the Mardiguian product and that of the instant mixture is statistically significant." On May 16, 1994, Aventis responded:

> "The results also demonstrate that different half lives were obtained for the claimed preparation versus the closest preparation for Mardiguian. **In particular, the half-live obtained for the claimed preparation was 4.36 +/1.07 hours whereas that for Mardiguian was 3.33 +/0.2 hours. This is approximately a 30% difference in results and is significant in that it means that the claimed preparations can be administered at significantly lower doses."**

On May 17, 1994, after another interview with the Examiner, Aventis filed a Supplemental Response and the Second Uzan Declaration. The Second Uzan Declaration presented five tables: Tables, I, X, and

XI which refer to the '618 patent and Tables A and III which refer to Mardiguian EP 40,144.

Table III "refer[s] to the compound of Mardiguian." Without mentioning dose amount, Table III reflects a mean half-life of 3.33 hours with a standard deviation of 0.82. Table X "refer[s] to the compound of the ['618 patent]." At a dose of 40 mg, it reflects a mean half-life of 4.36 hours with a standard deviation of 1.07. Table XI also "refer[s] to the compound of the ['618 patent]." At a dose of 60 mg, it reflects a mean half-life of 3.70 hours with a standard deviation of 0.82.

3. Amphastar's Contentions

Amphastar contends that Dr. Uzan's representations constituted a failure to disclose material information and an affirmative misrepresentation of a material fact. They constituted a failure to disclose material information because the unspecified dose amount in Table III was actually 60 mg and Dr. Uzan repeatedly[6] compared it to a disclosed 40 mg dose of the '618 patent. Comparing the 60 mg dose amount of Mardiguian 40,144 and the 60 mg dose amount of the '618 patent results in a much closer mean half-life.[7] It constituted an affirmative misrepresentation

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[6] The comparisons of the 40 mg dose of the '618 patent to the 40 mg dose of Mardiguian 40,144 were represented in paragraph (3) of Example 6, the May 17, 1994 Supplemental Response, the First Uzan Declaration, and the Second Uzan Declaration.

[7] This closer mean half-life is evident by comparing Table III with Table XI. Table III reported the half-life for Mardiguian EP 40,144 at a 60 mg dose as 3.33 hours with

[Footnote continued on next page]

of a material fact because Dr. Uzan's declarations affirmatively stated that the half-life of the '618 patent was improved over Mardiguian EP 40,144 while the data before him did not support such a conclusion.

Amphastar also contends Dr. Uzan should have disclosed to the Examiner additional evidence known to Dr. Uzan. This evidence establishes that had Dr. Uzan compared the same dose amounts, the '618 patent would not have been an improvement over Mardiguian EP 40,144 as to half-life. This evidence consists of the following studies.

The first study is a 1984 comparative study of the bioavailability of two salts of enoxaparin by M. Aiach and J.B. Fourtillian ("Aiach/Fourtillian Study").[8] The Aiach/Fourtillian Study included tests on PK 10169. This study is important because it formed the basis of Aventis' May 16, 1994 Amendment responding to the Examiner's objections and the Second Uzan Declaration. Among other things, the Aiach/Fourtillian Study contains the data that formed the basis of Table III, which reported the half-life for Mardiguian 40,144 as 3.33 hours with a standard deviation of 0.2. The Aiach/Fourtillian Study was conducted at a 60 mg dose. This dose was

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[Footnote continued from previous page]
a standard deviation of 0.2. Table XI reported the half-life for the '618 patent at a 60 mg dose as 3.70 hours with a standard deviation of 0.82.

[8] This study is different from Aiach, et al., A New Molecular Weight Heparin Derivative, 31 *Thrombosis Research* 611621 (1983).

not apparent from Table III, which was submitted with the Second Uzan Declaration.

The second study is Bara, et al., Comparative Pharmacokinetics of a Low Molecular Weight Heparin (PK 10169) ..., 39 *Thrombosis Research* 63136 (1985) ("Bara Study"). The Bara Study also conducted tests on PK 10169. Among other things, the Bara Study reported the mean half-life of a 40 mg dose of PK 10169 was 4.6 hours.[9] Dr. Uzan did not cite the Bara Study to the PTO during the prosecution of the '618 patent.

Bara also coauthored a related study with J. Dawes entitled Relationship Between Biological Activity and Concentration of a Low-Molecular-Weight Heparin (PK 10169) and Unfractionated Heparin after Intravenous and Subcutaneous Administration, 15 *Haemostasis* 116-122 (1986) ("Dawes Study"). Like the Bara Study, Dr. Uzan did not cite the Dawes Study to the PTO during the prosecution of the '618 patent. Among other things, the Dawes Study reported the half-life of a 40 mg dose of PK 10169 was 4.6 hours.[10]

The fourth study is a 1986 comparative study of the linear resorption of 4 doses of enoxaparin (20, 40, 60, and 80 mg) given as a single sub-cutaneous injection to twelve healthy individuals by J. Duchier and A. Frydman ("Duchier/Frydman Study"). The Duchier/Frydman Study compared different doses of the admixture which later became the '618 patent.

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[9] This was reported in the study as 275 minutes.

[10] This was reported in the study as 275 minutes.

Among other things, the Duchier/Frydman Study showed a mean half-life of 4.36 hours +/1.07 for a 40 mg dose and 3.70 hours +/.82 for a 60 mg dose. The 40 mg dose data was eventually included in Aventis' May 16, 1994 Amendment responding to the Examiner's objections and in the Second Uzan Declaration.

4. Elements of Inequitable Conduct

a. Affirmative Misrepresentation of a Material Fact, Failure to Disclose Material Information, or Submission of False Material Information

Inequitable conduct requires affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information. *Molins PLC*, 48 F.3d at 1178. 37 C.F.R. § 1.56 ("Section 1.56") defines factual materiality for which the PTO has promulgated the duty of disclosure. *Bruno Indep. Living Aids v. Acorn Mobility Servs.*, 394 F.3d 1348, 1352 (Fed. Cir. 2005) (citing *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997)). As defined in the current version of the rule,[11] information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and:

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[11] According to the PTO's notice of final rulemaking, the rule change applied to all applications pending or filed after March 16, 1992. Duty of Disclosure, 57 Fed. Reg. 2021 (Jan. 17, 1992). The '618 patent issued February 14, 1995. Therefore, the new rule was applicable during the prosecution of the '618 patent and the court evaluates the materiality under the standard set forth in the new rule.

> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
>
> > (i) Opposing an argument of unpatentability relied on by the Office, or
> >
> > (ii) Asserting an argument of patentability.

As discussed more fully above, through three Office Actions, the PTO rejected Aventis' claims because they were anticipated and obvious in view of Mardiguian EP 40,144. To overcome this bar to patentablility, Aventis repeatedly opposed the "argument of unpatentability relied on by the Office" and asserted an "argument of patentability" based on the purported improved half-life of the '618 patent over Mardiguian EP 40,144. These repeated representations satisfy materiality as defined in Section 1.56.

Aventis did not disclose that it derived the half-life data reported in paragraph (3) of Example 6, the May 17, 1994 Supplemental Response, the First Uzan Declaration, and the Second Uzan Declaration from a comparison of the Mardiguian LMWH at a different dose than the claimed LMWH. Moreover, Aventis did not disclose that a comparison of the same dosages did not yield significantly different half-lives. The Aiach/Fourtillian Study and the Duchier/Frydman Study show that Example 6 of the '618 patent was comparing 60 mg dose data of Mardiguian EP 40,144 to 40 mg dose data of the '618 patent. When Dr. Uzan submitted his two declarations affirmatively representing that there

was a "significant" difference in the half-life between Mardiguian EP 40,144 and the '618 patent, he was comparing a 60 mg dose of Mardiguian EP 40,144 to a 40 mg dose of the '618 patent. A comparison of Aiach/Fourtillian Study and the Duchier/Frydman Study indicates that a 60 mg dose of the '618 patent had a half-life of 3.70 hours +/.82 and a 60 mg dose of Mardiguian EP 40,144 had a half-life of 3.33 hours +/.69. Thus, Aventis compared different doses to show a difference in half-lives, but a comparison of available data regarding the same dose actually showed that there was little if any difference between the half-lives of Mardiguian EP 40,144 and the '618 patent.

Based on the foregoing, the court concludes that Amphastar, by clear and convincing evidence, has met "its initial burden of identifying for the court those portions of the materials on file that it believes demonstrates the absence of any genuine issue of material fact" with respect to Aventis' failure to disclose material information.[12] *See T.W. Elec. Serv., Inc.*, 809 F.2d at 630. Therefore, the burden of production now shifts to Aventis to establish "specific facts showing that there is a genuine issue for trial." *Id.*

Aventis opposes Amphastar's motion on four general grounds. First, Aventis contends that the studies and data cited by Amphastar were not Mardiguian EP 40,144 admixtures. Second, Aventis

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[12] As discussed more fully below, the court notes that in determining whether Amphastar met its initial burden, the court did not consider the Dawes Study and the Bara Study.

contends that errors in the half-life data of Example 6 actually favor the prior art. Third, Aventis contends that the Examiner considered the half-life data reported in Example 6 insignificant and relied only on comparison of mean half-lives derived from the underlying data. Finally, Aventis contends that Dr. Uzan told the Examiner that he was comparing different dosages. The court will consider each of these arguments.[13]

(i.) Prior Art Studies

As a preliminary matter, the court will first address the prior art studies of Dawes, Bara, Aiach/Fourtillan, and Frydman/Duchier because whether these studies are controverted will affect which evidence the court will consider when addressing the remaining arguments below.

Aventis contends that the LMWH tested in the studies were not Mardiguian EP 40,144 admixtures. Specifically, Aventis claims that Lot 573, the batch that is the subject of the Aiach/Fourtillan study was not an admixture prepared according to Mardiguian EP 40,144. Moreover, Aventis claims that Lot 930, the batch that is the subject of the Dawes Study and Bara Study, was also not prepared according to Mardiguian EP 40,144. Therefore, Aventis asserts that the Dawes and Bara Studies are not Mardiguian EP 40,144 products and the court should not

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[13] The court notes that Aventis also opposes Amphastar's motion on the ground that Dr. Uzan's comparison of half-lives at different dosages was reasonable. The court will address this argument in the intent section below.

consider the half-lives reported in the Dawes and Bara Studies as reflecting the half-lives of Mardiguian EP 40,144.

The court concludes based on evidence submitted by Aventis that a reasonable jury could find that the Dawes and Bara Studies were not prepared according to Mardiguian EP 40,144. *See Anderson*, 477 U.S. at 252, 106 S.Ct. 2505. Due to this controverted fact, the court concludes that whether the omission of the Dawes and Bara Studies constituted a failure to disclose material information is a genuine issue of fact. *See Molins PLC*, 48 F.3d at 1178. The court therefore will not consider the half-lives reported in the Dawes and Bara Studies.

It is uncontroverted that the Aiach/Fourtillan study is the source of the data in paragraph (3) of Example 6 of the '618 patent, as well as Table III attached to the Second Uzan Declaration filed during the prosecution of the '618 patent. Example 6 of the '618 patent specifically states that the data in paragraph (3) relates to Mardiguian 40,144. Moreover, it is uncontroverted that the Frydman/Duchier study is described in Example 6 of the '618 patent, and is the source of the data in paragraph (1) of Example 6 and Tables X and XI in the Second Uzan Declaration.

It is uncontroverted that Aventis represented to the PTO that the Aiach/Fourtillan Study relates to the Mardiguian EP 40,144, and it is further uncontroverted that the Aiach/Fourtillan Study relates to the Mardiguian EP 40,144. The court will also consider the Frydman/Duchier study because it is factually undisputed that it is the source of data represented in the '618 patent. The court will not

however, consider the Dawes and Bara studies for any purpose.

(ii.) Errors in the Half-Life Data of Example 6 Favor the Prior Art and Militate Against Patentability

Aventis contends that errors in the half-life data of Example 6 favor the prior art. Specifically, Aventis contends that Subparagraphs (1), (3) and (4) of Example 6 admittedly contain errors in the reported percentages of patients having the specified half-lives. For example, subparagraph (3) purports to state the percentage of cases having a half-life longer than 4 1/2 hours, which, if reported correctly, would be 0%. However, subparagraph (3) reports 17%, which favors the Mardiguian EP 40,144 admixture for half life longer than 4 1/2 hours. Therefore, Aventis concludes that while Example 6 has errors, those errors would actually militate against patentability because they erred in Mardiguian EP 40,144's favor.

Aventis' contention fails because it depends on the assumption that an increase in dose yields a longer half-life. Yet, Aventis submits no evidence that in the context of Mardiguian EP 40,144 or the '618 patent, half-life increases with doses between 40 mg and 60 mg. The closest Aventis comes to producing such evidence is Dr. Uzan's statement that "the probability of having higher pharmacological parameters is higher with a higher dose than it is with a lower dose." This general statement does not create a genuine issue of material fact because it is not specific, is unconnected to the Mardiguian patent or LMWHs in general, and is contradicted by other credible evidence. *Univ. of W. Va. v. Van Voorhies*, 278 F.3d 1288, 1299 (Fed. Cir. 2002) ("[S]elf-serving,

uncorroborated [evidence] do[es] not create a genuine issue of material fact to preclude summary judgment in light of the overwhelming evidence and admissions"). The Frydman/Duchier Study which studied the '618 patent indicates that half-life does not increase with doses between 40 mg and 60 mg. The Frydman/Duchier Study reported half-life by dose as follows:

Dose	Mean +/Standard Deviation
20 mg	4.18 +/2.21h
40 mg	4.36 +/1.07h
60 mg	3.70 +/0.82h
80 mg	3.46 +/0.86h

This table shows that the half-life for a 60 mg dose is approximately 0.66 hours less than for a 40 mg dose. Moreover, the half-life for a 60 mg dose of Mardiguian 40,144 is 3.33 hours +/.69, which suggests that Mardiguian 40,144's half-life is not significantly different than the '618 patent. In sum, because Aventis submits no evidence from which a reasonable jury could find that the 60 mg dose favored Mardiguian 40,144, Aventis does not create a genuine issue of material fact that its error, namely omitting the dosage of Mardiguian 40,144, militates against patentability. Based on the evidence before the court, comparing the 60 mg dose of Mardiguian with the 40 mg dose of the '618 patent actually militates in favor of patentability.

(iii.) Significance of Example 6

Aventis contends that the Examiner considered the half-life data reported in Example 6 insignificant and relied only on comparison of mean half-lives derived from the underlying data. In support of this claim, Aventis cites the Second Uzan Declaration,

which abandoned the percentage calculations of the compared half-lives and focused instead on the means of the compared half-lives. Therefore, based on the Second Uzan Declaration, Aventis concludes "the patentee exclusively relied on comparisons of mean half-life data calculated from the entire set of patient data at a given dose for distinguishing the Mardiguian [40,144]."

Aventis' argument that the Examiner "declined to rely on the half-life percentages reported in Example 6 and the comparison by Dr. Uzan in his declaration" is essentially an argument that such prior representations are not material.[14] In the context of inequitable conduct, materiality is defined in Section 1.56. In relevant part, Section 1.56 defines material information as noncumulative information that opposes an argument of unpatentability relied on by the PTO or asserts an argument of patentability. As discussed above, Example 6 purports to "illustrate[ ] the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life." This is an argument of patentablility. Thus, as defined by Section 1.56, Example 6 is material.

Moreover, the Federal Circuit has made clear that for a misrepresentation to be material, it "need not be relied on by the examiner in deciding to allow the patent. The matter misrepresented need only be within a reasonable examiner's realm of

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[14] Noteworthy is the lack of evidence to support Aventis' claim of non-reliance by the Examiner. This contention appears grounded in speculation.

consideration." *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1421 (Fed. Cir. 1989). Section 1.56 does not state, and Aventis cites no law suggesting, that evidence which is material under section 1.56 can become immaterial because the patent applicant submitted subsequent non-cumulative information in support of patentability or in opposition to an argument of unpatentability. The fact that Aventis submitted data reflecting the mean half-lives of the LMWHs does not indicate that the Examiner stopped relying on the percentages. Indeed, in an amendment filed by Aventis on June 1, 1994, Aventis called the subsequent data "additional data," which indicates that it was not cumulative. Further, the amendment only reported the same data in a different manner. Finally, even if the Examiner relied only on the reported mean half-lives, this does not render Example 6 irrelevant because Aventis continued to use the same underlying data-a 60 mg Mardiguian EP 40,144 dose and a 40 mg '618 patent dose-to establish the same point, mainly that the '618 patent showed a "substantial" improvement in half-life over Mardiguian EP 40,144.

(iv.) Dr. Uzan's Disclosures to the Examiner

Aventis contends that Dr. Uzan disclosed to the PTO that he used different dosages in comparing the half-lives of the Mardiguian and Debric admixtures. In support of this contention, Aventis submits the First Uzan Declaration and an Amendment filed on June 1, 1994. The First Uzan Declaration states:

> "[T]he claimed formulations have also been compared with those set forth in Mardiguian, European Patent 0,040,144. As discussed therein, the claimed formulations had a

> plasma half life longer than 4 1/2 hours in 45% of the cases in contrast to Mardiguan who achieved such a half life in only 17% of the cases. **This represents an increase in 250% in the half life and is very significant because it enables the same effect to be achieved with lower dosages.**" (emphasis added)

An Amendment filed by Aventis on June 1, 1994, similarly states:

> "As for results obtained by applicant, it is noted that the Patent Office is concerned that the evidence provided to date by applicant to distinguish his invention from the applied prior art is not statistically significant. To this end, additional data has been provided setting forth the sampling from which the data relied upon by applicant was obtained. The results also demonstrate that different half-lives were obtained for the claimed preparation versus the closest preparation of Mardiguian. In particular, the half life obtained for the claimed preparation was 4.36 +/1 1.07 hours where as that for Mardiguian was 3.33 +/0.2. **This is approximately a 30% difference in results and is significant in that it means that the claimed preparations can be administered in significantly lower doses."** (emphasis added).

Aventis also submits the deposition of Dr. Uzan. In the deposition, Dr. Uzan interprets his statement in his first declaration as "say[ing] the comparison is a comparison between two doses of which one is lower than the other."

With respect to the First Uzan Declaration and the June 1, 1994 Amendment, neither of these statements can reasonably be interpreted as meaning that the half-life data was based upon different dosages. The two documents purportedly compare the '618 patent and Mardiguian EP 40,144 to reveal a "significant" difference in response to a lack of statistical significance from prior art. In other words, the language in these documents means that the comparison between these two admixtures is significant because the results establish that one can be administered at a lower dose than the other. It is not an illustration of application at a lower dose. It is "significant ... because it enables" administration of the LMWH at a lower dose.

Dr. Uzan's statement in his deposition interpreting the First Uzan Declaration is specious and cannot create a genuine issue of material fact. *See Van Voorhies*, 278 F.3d at 1299. It is clear from the documentary evidence that there is no suggestion that the data was obtained from preparations at different doses. Dr. Uzan concedes as much:

> Question: Do you, anywhere in Exhibit 16 [First Uzan Declaration], tell the Examiner that the Mardiguian formulations which you are reciting data for in the second sentence involve a 60 milligram dose?
>
> Answer: No, my declaration is not specific to that degree.

b. Intent to Deceive the PTO

Inequitable conduct requires intent to deceive the PTO. *See Molins PLC*, 48 F.3d at 1178. If the materiality of a misrepresentation of a material fact is high, then a lesser showing of intent can be

sufficient. *See Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1381 (Fed. Cir. 2001). "Intent need not, and rarely can, be proven by direct evidence." *Merck & Co., Inc.*, 873 F.2d at 1422 (Fed. Cir. 1989). Rather, in the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information. *See Paragon Podiatry Lab., Inc. v. KLM Labs. Inc.*, 984 F.2d 1182, 1193 (Fed. Cir. 1993).

(i.) High Materiality

Aventis' representations regarding half life during prosecution of the '618 patent made the purported significantly improved half-life highly material to patentability. As discussed above, Aventis referred the Examiner to the increased half-life established in Example 6 of the '618 patent in response to a rejection of obviousness. On August 3, 1992, in response to the Examiner's contention that the comparative data in Example 6 was not persuasive, Aventis reiterated its position that '618 was patentable over Mardiguian EP 40,144 because of the purported increase in half-life. The PTO was not persuaded. On April 16, 1993, Aventis submitted evidence purporting to show a 250% increase in half-life. Aventis also submitted the First Uzan Declaration and represented a "very significant" increase in half life. The Examiner again rejected Aventis claims because Aventis "failed to provide evidence that the alleged difference between the half-life of the Mardiguian product and that of the instant mixture is statistically significant." Thereafter, on November 20, 1993, Aventis made the further representation that:

> [D]ifferent half lives were obtained for the claimed preparation versus the closest preparation for Mardiguian. In particular, the half-life obtained for the claimed preparation was 4.36 +/1.07 hours whereas that for Mardiguian was 3.33 +/0.2 hours. This is approximately a 30% difference in results and is significant in that it means that the claimed preparations can be administered at significantly lower doses.

Aventis' representations satisfied Section 1.56 as to materiality. Aventis referred to the purported improved half-life of the '618 patent on at least four occasions in opposition to "argument[s] of unpatentability relied on by the Office" and asserted an "argument of patentability" based on the improved half-life of the '618 patent over Mardiguian EP 40,144. These repeated representations establish that Aventis created high materiality for half-life. Militating even further in favor of a high materiality is the fact that the Examiner allowed the patent after the last representation purporting to establish a statistically significant improvement in half-life based on the half-live obtained for the '618 patent, which was 4.36 +/1.07 hours, whereas that for Mardiguian EP 40,144 was 3.33 +/0.2 hours.

(ii.) Credible Explanation

Aventis contends that Dr. Uzan's comparison of half-lives at different dosages was reasonable and it provides a variety of explanations. Essentially relying on a contention above-that errors in the half-life data of Example 6 actually favor the prior art Dr. Uzan stated in his deposition:

> "So, in this case, I gave preference to Mardiguian product in selecting the dose

> that I selected which was the higher dose than the Debrie dose. If I had done the opposite, I would have, to some extent, given an advantage to the Debrie admixture, but I did not. On the contrary, I gave advantage to the [Mardiguian patent], so there is nothing abnormal there."

In addition to this alleged advantage, Aventis also argues that it chose to use the 40 mg dose of the '618 patent because the 60 mg dose caused bleeding in postoperative patients. Finally, Aventis argues that the 60 mg dose in the Frydman/Duchier Study was not confirmed while the 40 mg dose was confirmed in a separate study. Based on these three grounds, Aventis asserts that Dr. Uzan's comparison of half-lives at different dosages was reasonable and thus a credible explanation for the omission.

Aventis' contention fails generally because the question is not whether use of the 40 mg dose was reasonable. The issue is whether Dr. Uzan's two declarations, which affirmatively represented that there was a "significant" difference in the half-life between Mardiguian EP 40,144 and the '618 patent by comparing a 60 mg dose of the Mardiguian patent to a 40 mg dose of the '618 patent, was an omission of a material fact, especially in light of the fact that the same study showed the 60 mg dose of the '618 patent established that the half-lives were much closer.

Aventis' specific arguments also fail. As discussed more fully above, other than Dr. Uzan's unsupported and general claim, Aventis submits no evidence that the 60 mg dose gave preference to Mardiguian EP 40,144. Finally, Dr. Uzan's explanations-that he chose to use the 40 mg dose of the '618 patent because the 60 mg dose caused

bleeding in post-operative patients and that the 60 mg dose was not verified-are not persuasive because he used the same 60 mg dose in paragraph (1) of Example 6.

(iii.) Facts and Circumstances Surrounding Failure to Disclose Material Information

The facts and circumstances surrounding the failure to disclose the dose differential militate in favor of Aventis' intent to deceive. By comparing different doses, Aventis represented to the Examiner that the half-life "obtained for the claimed preparation was 4.36 +/1.07 hours whereas that for Mardiguian was 3.33 +/0.2 hours. This is approximately a 30% difference in results and is significant in that it means that the claimed preparations can be administered at significantly lower doses." Indeed, had the 60 mg dose of Mardiguian been compared to the 60 mg dose of the '618 patent, results would have indicated that the mean half-life for the '618 patent was 3.70 +/0.82 hours and the mean half-life for Mardiguian EP 40,144 was 3.33 +/0.2 hours. Whether the Examiner would have concluded that this difference in half-life would "distinguish [the] invention from the applied prior art" in a statistically significant way is unknown. It is unknown because Aventis deprived the Examiner of this opportunity by repeatedly misrepresenting the evidence. This foregoing fact supports a strong inference of intent by Aventis to deceive the PTO. *See Paragon*, 984 F.2d at 1182.

c. Weighing Materiality and Intent

The court must weigh materiality and intent "to determine if equity warrants a finding of inequitable conduct." *Ulead Sys., Inc.*, 351 F.3d at 1144. Based on the totality of the circumstances, including

Amphastar's weighty uncontroverted evidence establishing materiality and intent to deceive and Aventis' scintilla of evidence in opposition thereto, the court concludes that no genuine issues of material fact exist and Amphastar is entitled, as a matter of law and equity, to summary judgment against Aventis on its affirmative defense and counterclaim based on inequitable conduct. As a result, the '618 patent is unenforceable.[15] *See Ulead Sys., Inc.*, 351 F.3d at 1144.

IV.

DISPOSITION

ACCORDINGLY, IT IS ORDERED:

(1) Defendant Amphastar Pharmaceuticals, Inc.'s motion for summary judgment based on inequitable conduct is GRANTED;

(2) Defendant Amphastar Pharmaceuticals, Inc.'s motion for summary judgment of invalidity based on indefiniteness is DENIED as moot;

(3) Defendant Amphastar Pharmaceuticals, Inc.'s motion for summary judgment of invalidity pursuant to 35 U.S.C. § 102 is DENIED as moot.

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[15] By reason of having granted Amphastar's motion for summary judgment based on inequitable conduct, the court will deny as moot Amphastar's remaining motions for summary judgment, namely Amphastar's motion for summary judgment of invalidity based on indefiniteness and Amphastar's motion for summary judgment of invalidity based on 35 U.S.C. § 102.